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# Complex speech-language therapy interventions for stroke-related aphasia: the RELEASE study incorporating a systematic review and individual participant data network meta-analysis

*Marian C Brady, Myzoon Ali, Kathryn VandenBerg, Linda J Williams, Louise R Williams, Masahiro Abo, Frank Becker, Audrey Bowen, Caitlin Brandenburg, Caterina Breitenstein, Stefanie Bruehl, David A Copland, Tamara B Cranfill, Marie di Pietro-Bachmann, Pamela Enderby, Joanne Fillingham, Federica Lucia Galli, Marialuisa Gandolfi, Bertrand Glize, Erin Godecke, Neil Hawkins, Katerina Hilari, Jacqueline Hinckley, Simon Horton, David Howard, Petra Jaecks, Elizabeth Jefferies, Luis MT Jesus, Maria Kambanaros, Eun Kyoung Kang, Eman M Khedr, Anthony Pak-Hin Kong, Tarja Kukkonen, Marina Laganaro, Matthew A Lambon Ralph, Ann Charlotte Laska, Béatrice Leemann, Alexander P Leff, Roxele R Lima, Antje Lorenz, Brian MacWhinney, Rebecca Shisler Marshall, Flavia Mattioli, İlknur Maviş, Marcus Meinzer, Reza Nilipour, Enrique Noé, Nam-Jong Paik, Rebecca Palmer, Ilias Papathanasiou, Brígida F Patrício, Isabel Pavão Martins, Cathy Price, Tatjana Prizl Jakovac, Elizabeth Rochon, Miranda L Rose, Charlotte Rosso, Ilona Rubi-Fessen, Marina B Ruiter, Claerwen Snell, Benjamin Stahl, Jerzy P Szaflarski, Shirley A Thomas, Mieke van de Sandt-Koenderman, Ineke van der Meulen, Evy Visch-Brink, Linda Worrall and Heather Harris Wright*





# Complex speech-language therapy interventions for stroke-related aphasia: the RELEASE study incorporating a systematic review and individual participant data network meta-analysis

Marian C Brady<sup>1\*</sup> Myzoon Ali<sup>1</sup>  
Kathryn VandenBerg<sup>1</sup> Linda J Williams<sup>2</sup>  
Louise R Williams<sup>1</sup> Masahiro Abo<sup>3</sup> Frank Becker<sup>4,5</sup>  
Audrey Bowen<sup>6</sup> Caitlin Brandenburg<sup>7</sup>  
Caterina Breitenstein<sup>8</sup> Stefanie Bruehl<sup>9,10,11</sup>  
David A Copland<sup>7</sup> Tamara B Cranfill<sup>12</sup>  
Marie di Pietro-Bachmann<sup>13</sup> Pamela Enderby<sup>14</sup>  
Joanne Fillingham<sup>15</sup> Federica Lucia Galli<sup>16</sup>  
Marialuisa Gandolfi<sup>17</sup> Bertrand Glize<sup>18,19</sup>  
Erin Godecke<sup>20</sup> Neil Hawkins<sup>21</sup> Katerina Hilari<sup>22</sup>  
Jacqueline Hinckley<sup>23</sup> Simon Horton<sup>24</sup>  
David Howard<sup>25</sup> Petra Jaecks<sup>26</sup> Elizabeth Jefferies<sup>27</sup>  
Luis MT Jesus<sup>28</sup> Maria Kambanaros<sup>29</sup>  
Eun Kyoung Kang<sup>30</sup> Eman M Khedr<sup>31</sup>  
Anthony Pak-Hin Kong<sup>32</sup> Tarja Kukkonen<sup>33</sup>  
Marina Laganaro<sup>34</sup> Matthew A Lambon Ralph<sup>35</sup>  
Ann Charlotte Laska<sup>36</sup> Béatrice Leemann<sup>37</sup>  
Alexander P Leff<sup>38</sup> Roxele R Lima<sup>39</sup> Antje Lorenz<sup>40</sup>  
Brian MacWhinney<sup>41</sup> Rebecca Shisler Marshall<sup>42</sup>  
Flavia Mattioli<sup>43</sup> İlknur Maviş<sup>44</sup> Marcus Meinzer<sup>45</sup>  
Reza Nilipour<sup>46</sup> Enrique Noé<sup>47</sup> Nam-Jong Paik<sup>48</sup>  
Rebecca Palmer<sup>14</sup> Ilias Papathanasiou<sup>49</sup>  
Brígida F Patrício<sup>50</sup> Isabel Pavão Martins<sup>51</sup>  
Cathy Price<sup>52</sup> Tatjana Prizl Jakovac<sup>53</sup>  
Elizabeth Rochon<sup>54,55</sup> Miranda L Rose<sup>56,57</sup>  
Charlotte Rosso<sup>58</sup> Ilona Rubi-Fessen<sup>59</sup>

Marina B Ruiter<sup>id,60</sup> Claerwen Snell<sup>id,61</sup>  
Benjamin Stahl<sup>id,62</sup> Jerzy P Szaflarski<sup>id,63</sup>  
Shirley A Thomas<sup>id,64</sup>  
Mieke van de Sandt-Koenderman<sup>id,65,66</sup>  
Ineke van der Meulen<sup>id,65,66</sup> Evy Visch-Brink<sup>id,67</sup>  
Linda Worrall<sup>id,7</sup> and Heather Harris Wright<sup>id,68</sup>

<sup>1</sup>Nursing Midwifery and Allied Health Professions Unit, Glasgow Caledonian University, Glasgow, UK

<sup>2</sup>The Usher Institute, University of Edinburgh, Edinburgh, UK

<sup>3</sup>Department of Rehabilitation Medicine, The Jikei University School of Medicine, Tokyo, Japan

<sup>4</sup>Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

<sup>5</sup>Sunnaas Rehabilitation Hospital, Nesoddtangen, Norway

<sup>6</sup>Geoffrey Jefferson Brain Research Centre, The Manchester Academic Health Science Centre, Northern Care Alliance & University of Manchester, Manchester, UK

<sup>7</sup>School of Health and Rehabilitation Sciences, The University of Queensland, Brisbane, QLD, Australia

<sup>8</sup>Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany

<sup>9</sup>St Mauritius Rehabilitation Centre, Meerbusch, Germany

<sup>10</sup>Clinical and Cognitive Neurosciences, Department of Neurology, Medical Faculty, RWTH Aachen University, Aachen, Germany

<sup>11</sup>Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, UK

<sup>12</sup>Special Education, Eastern Kentucky University, Richmond, KY, USA

<sup>13</sup>Division of Neurorehabilitation, Department of Clinical Neurosciences, University Hospitals and University of Geneva, Geneva, Switzerland

<sup>14</sup>School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK

<sup>15</sup>Nursing Directorate, NHS Improvement, London, UK

<sup>16</sup>Neurorehabilitation Clinic, Neurological Sciences Department, Marche Polytechnic University, Ospedali Riuniti di Ancona, Ancona, Italy

<sup>17</sup>Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

<sup>18</sup>EA 4136 Handicap Activity Cognition Health, University of Bordeaux, Bordeaux, France

<sup>19</sup>Department of Physical Medicine and Rehabilitation, Centre Hospitalier Universitaire (CHU) de Bordeaux, Bordeaux, France

<sup>20</sup>School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia

<sup>21</sup>Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK

<sup>22</sup>Division of Language and Communication Science, City, University of London, London, UK

- <sup>23</sup>Nova Southeastern University, Fort Lauderdale, FL, USA
- <sup>24</sup>School of Health Sciences, University of East Anglia, Norwich, UK
- <sup>25</sup>School of Education Communication and Language Sciences, Newcastle University, Newcastle Upon Tyne, UK
- <sup>26</sup>Faculty of Linguistics and Literary Studies, Bielefeld University, Bielefeld, Germany
- <sup>27</sup>Department of Psychology, University of York, York, UK
- <sup>28</sup>School of Health Sciences (ESSUA) and Institute of Electronics and Informatics Engineering of Aveiro (IEETA), University of Aveiro, Aveiro, Portugal
- <sup>29</sup>Department of Rehabilitation Sciences, Cyprus University of Technology, Limassol, Cyprus
- <sup>30</sup>Department of Rehabilitation Medicine, Kangwon National University Hospital, Gangwon-do, Republic of Korea
- <sup>31</sup>Department of Neurology, Assiut University Hospital, Assiut, Egypt
- <sup>32</sup>School of Communication Sciences and Disorders, University of Central Florida, Orlando, FL, USA
- <sup>33</sup>Ear, Nose and Throat (ENT)/Department of Phoniatriy, Tampere University Hospital, Tampere, Finland
- <sup>34</sup>Faculty of Psychology and Educational Science, University of Geneva, Geneva, Switzerland
- <sup>35</sup>Medical Research Council Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK
- <sup>36</sup>Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden
- <sup>37</sup>Neuroréducation, Département des Neurosciences Cliniques, Hôpitaux Universitaires de Genève, Geneva, Switzerland
- <sup>38</sup>Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, UK
- <sup>39</sup>Department of Speech Language Pathology, Educational Association Bom Jesus – IELUSC, Santa Catarina, Brazil
- <sup>40</sup>Institut für Psychologie, Humboldt University Berlin, Berlin, Germany
- <sup>41</sup>Department of Psychology, Carnegie Mellon University, Pittsburgh, PA, USA
- <sup>42</sup>Department of Communication Sciences and Special Education, University of Georgia, Athens, GA, USA
- <sup>43</sup>Neuropsychology Unit, Azienda Socio Sanitaria Territoriale (ASST), Brescia via Nikolajewka 13, Italy
- <sup>44</sup>Department of Speech and Language Therapy, Anadolu University, Eskişehir, Turkey
- <sup>45</sup>UQ Centre for Clinical Research, The University of Queensland, Brisbane, QLD, Australia
- <sup>46</sup>Department of Speech Therapy, University of Social Welfare and Rehabilitation Sciences, Tehran, Islamic Republic of Iran
- <sup>47</sup>NEURORHB-Hospitales Vithas, Valencia, Spain
- <sup>48</sup>Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
- <sup>49</sup>Department of Speech and Language Therapy, Technological Educational Institute of Western Greece, Patras, Greece
- <sup>50</sup>Speech Therapy Department of Health School of Polytechnic Institute of Porto, Porto, Portugal
- <sup>51</sup>Laboratório de Estudos de Linguagem, Faculdade de Medicina de Lisboa, Universidade de Lisboa, Lisbon, Portugal

- <sup>52</sup>Wellcome Centre for Human Neuroimaging, University College London, London, UK
- <sup>53</sup>Department of Speech and Language Pathology, Faculty of Education and Rehabilitation Sciences, University of Zagreb, Zagreb, Croatia
- <sup>54</sup>Department of Speech–Language Pathology and Rehabilitation Sciences Institute, University of Toronto, Toronto, ON, Canada
- <sup>55</sup>Toronto Rehabilitation Institute, Toronto, ON, Canada
- <sup>56</sup>School of Allied Health, Human Services and Sport, La Trobe University, Melbourne, VIC, Australia
- <sup>57</sup>Centre of Research Excellence in Aphasia Recovery and Rehabilitation, La Trobe University, Melbourne, VIC, Australia
- <sup>58</sup>Institut du Cerveau (Paris Brain Institute), Sorbonne Université, ICM, Inserm, CNRS, AP-HP, Hôpital Salpêtrière, Stroke Unit, DMU Neuroscience 6, Paris, France
- <sup>59</sup>RehaNova Rehabilitation Hospital and Department of Special Education and Rehabilitation, University of Cologne, Cologne, Germany
- <sup>60</sup>Sint Maartenskliniek, Rehabilitation Centre and Centre for Language Studies, Radboud University, Nijmegen, the Netherlands
- <sup>61</sup>Warrington Hospital, Warrington and Halton NHS Foundation Trust, Warrington, UK
- <sup>62</sup>Department of Neurology, Charité Universitätsmedizin Berlin, Berlin, Germany
- <sup>63</sup>UAB Epilepsy Centre, Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA
- <sup>64</sup>Division of Rehabilitation, Ageing and Wellbeing, School of Medicine, University of Nottingham, Nottingham, UK
- <sup>65</sup>Rijndam Rehabilitation, Rotterdam, the Netherlands
- <sup>66</sup>Department of Rehabilitation Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
- <sup>67</sup>Department of Neurology and Neurosurgery, Erasmus University Medical Center, Rotterdam, the Netherlands
- <sup>68</sup>College of Allied Health Sciences, East Carolina University, Greenville, SC, USA

\*Corresponding author

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# Abstract

## Complex speech-language therapy interventions for stroke-related aphasia: the RELEASE study incorporating a systematic review and individual participant data network meta-analysis

Marian C Brady<sup>1\*</sup>, Myzoon Ali<sup>1</sup>, Kathryn Vandenberg<sup>1</sup>, Linda J Williams<sup>2</sup>, Louise R Williams<sup>1</sup>, Masahiro Abo<sup>3</sup>, Frank Becker<sup>4,5</sup>, Audrey Bowen<sup>6</sup>, Caitlin Brandenburg<sup>7</sup>, Caterina Breitenstein<sup>8</sup>, Stefanie Bruehl<sup>9,10,11</sup>, David A Copland<sup>7</sup>, Tamara B Cranfill<sup>12</sup>, Marie di Pietro-Bachmann<sup>13</sup>, Pamela Enderby<sup>14</sup>, Joanne Fillingham<sup>15</sup>, Federica Lucia Galli<sup>16</sup>, Marialuisa Gandolfi<sup>17</sup>, Bertrand Glize<sup>18,19</sup>, Erin Godecke<sup>20</sup>, Neil Hawkins<sup>21</sup>, Katerina Hilari<sup>22</sup>, Jacqueline Hinckley<sup>23</sup>, Simon Horton<sup>24</sup>, David Howard<sup>25</sup>, Petra Jaecks<sup>26</sup>, Elizabeth Jefferies<sup>27</sup>, Luis MT Jesus<sup>28</sup>, Maria Kambanaros<sup>29</sup>, Eun Kyoung Kang<sup>30</sup>, Eman M Khedr<sup>31</sup>, Anthony Pak-Hin Kong<sup>32</sup>, Tarja Kukkonen<sup>33</sup>, Marina Laganaro<sup>34</sup>, Matthew A Lambon Ralph<sup>35</sup>, Ann Charlotte Laska<sup>36</sup>, Béatrice Leemann<sup>37</sup>, Alexander P Leff<sup>38</sup>, Roxele R Lima<sup>39</sup>, Antje Lorenz<sup>40</sup>, Brian MacWhinney<sup>41</sup>, Rebecca Shisler Marshall<sup>42</sup>, Flavia Mattioli<sup>43</sup>, İlknur Maviş<sup>44</sup>, Marcus Meinzer<sup>45</sup>, Reza Nilipour<sup>46</sup>, Enrique Noé<sup>47</sup>, Nam-Jong Paik<sup>48</sup>, Rebecca Palmer<sup>14</sup>, Ilias Papathanasiou<sup>49</sup>, Brígida F Patrício<sup>50</sup>, Isabel Pavão Martins<sup>51</sup>, Cathy Price<sup>52</sup>, Tatjana Prizl Jakovac<sup>53</sup>, Elizabeth Rochon<sup>54,55</sup>, Miranda L Rose<sup>56,57</sup>, Charlotte Rosso<sup>58</sup>, Ilona Rubi-Fessen<sup>59</sup>, Marina B Rüter<sup>60</sup>, Claerwen Snell<sup>61</sup>, Benjamin Stahl<sup>62</sup>, Jerzy P Szaflarski<sup>63</sup>, Shirley A Thomas<sup>64</sup>, Mieke van de Sandt-Koenderman<sup>65,66</sup>, Ineke van der Meulen<sup>65,66</sup>, Evy Visch-Brink<sup>67</sup>, Linda Worrall<sup>7</sup> and Heather Harris Wright<sup>68</sup>

<sup>1</sup>Nursing Midwifery and Allied Health Professions Unit, Glasgow Caledonian University, Glasgow, UK

<sup>2</sup>The Usher Institute, University of Edinburgh, Edinburgh, UK

<sup>3</sup>Department of Rehabilitation Medicine, The Jikei University School of Medicine, Tokyo, Japan

<sup>4</sup>Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

<sup>5</sup>Sunnaas Rehabilitation Hospital, Nesoddtangen, Norway

<sup>6</sup>Geoffrey Jefferson Brain Research Centre, The Manchester Academic Health Science Centre, Northern Care Alliance & University of Manchester, Manchester, UK

<sup>7</sup>School of Health and Rehabilitation Sciences, The University of Queensland, Brisbane, QLD, Australia

- <sup>8</sup>Department of Neurology with Institute of Translational Neurology, University of Münster, Münster, Germany
- <sup>9</sup>St Mauritius Rehabilitation Centre, Meerbusch, Germany
- <sup>10</sup>Clinical and Cognitive Neurosciences, Department of Neurology, Medical Faculty, RWTH Aachen University, Aachen, Germany
- <sup>11</sup>Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, UK
- <sup>12</sup>Special Education, Eastern Kentucky University, Richmond, KY, USA
- <sup>13</sup>Division of Neurorehabilitation, Department of Clinical Neurosciences, University Hospitals and University of Geneva, Geneva, Switzerland
- <sup>14</sup>School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK
- <sup>15</sup>Nursing Directorate, NHS Improvement, London, UK
- <sup>16</sup>Neurorehabilitation Clinic, Neurological Sciences Department, Marche Polytechnic University, Ospedali Riuniti di Ancona, Ancona, Italy
- <sup>17</sup>Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy
- <sup>18</sup>EA 4136 Handicap Activity Cognition Health, University of Bordeaux, Bordeaux, France
- <sup>19</sup>Department of Physical Medicine and Rehabilitation, Centre Hospitalier Universitaire (CHU) de Bordeaux, Bordeaux, France
- <sup>20</sup>School of Medical and Health Sciences, Edith Cowan University, Perth, WA, Australia
- <sup>21</sup>Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK
- <sup>22</sup>Division of Language and Communication Science, City, University of London, London, UK
- <sup>23</sup>Nova Southeastern University, Fort Lauderdale, FL, USA
- <sup>24</sup>School of Health Sciences, University of East Anglia, Norwich, UK
- <sup>25</sup>School of Education Communication and Language Sciences, Newcastle University, Newcastle Upon Tyne, UK
- <sup>26</sup>Faculty of Linguistics and Literary Studies, Bielefeld University, Bielefeld, Germany
- <sup>27</sup>Department of Psychology, University of York, York, UK
- <sup>28</sup>School of Health Sciences (ESSUA) and Institute of Electronics and Informatics Engineering of Aveiro (IEETA), University of Aveiro, Aveiro, Portugal
- <sup>29</sup>Department of Rehabilitation Sciences, Cyprus University of Technology, Limassol, Cyprus
- <sup>30</sup>Department of Rehabilitation Medicine, Kangwon National University Hospital, Gangwon-do, Republic of Korea
- <sup>31</sup>Department of Neurology, Assiut University Hospital, Assiut, Egypt
- <sup>32</sup>School of Communication Sciences and Disorders, University of Central Florida, Orlando, FL, USA
- <sup>33</sup>Ear, Nose and Throat (ENT)/Department of Phoniatria, Tampere University Hospital, Tampere, Finland
- <sup>34</sup>Faculty of Psychology and Educational Science, University of Geneva, Geneva, Switzerland
- <sup>35</sup>Medical Research Council Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK
- <sup>36</sup>Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden
- <sup>37</sup>Neurorééducation, Département des Neurosciences Cliniques, Hôpitaux Universitaires de Genève, Geneva, Switzerland
- <sup>38</sup>Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, UK
- <sup>39</sup>Department of Speech Language Pathology, Educational Association Bom Jesus – IELUSC, Santa Catarina, Brazil
- <sup>40</sup>Institut für Psychologie, Humboldt University Berlin, Berlin, Germany
- <sup>41</sup>Department of Psychology, Carnegie Mellon University, Pittsburgh, PA, USA
- <sup>42</sup>Department of Communication Sciences and Special Education, University of Georgia, Athens, GA, USA
- <sup>43</sup>Neuropsychology Unit, Azienda Socio Sanitaria Territoriale (ASST), Brescia via Nikolajewka 13, Italy
- <sup>44</sup>Department of Speech and Language Therapy, Anadolu University, Eskişehir, Turkey
- <sup>45</sup>UQ Centre for Clinical Research, The University of Queensland, Brisbane, QLD, Australia
- <sup>46</sup>Department of Speech Therapy, University of Social Welfare and Rehabilitation Sciences, Tehran, Islamic Republic of Iran
- <sup>47</sup>NEURORHB-Hospitales Vithas, Valencia, Spain

- <sup>48</sup>Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
- <sup>49</sup>Department of Speech and Language Therapy, Technological Educational Institute of Western Greece, Patras, Greece
- <sup>50</sup>Speech Therapy Department of Health School of Polytechnic Institute of Porto, Porto, Portugal
- <sup>51</sup>Laboratório de Estudos de Linguagem, Faculdade de Medicina de Lisboa, Universidade de Lisboa, Lisbon, Portugal
- <sup>52</sup>Wellcome Centre for Human Neuroimaging, University College London, London, UK
- <sup>53</sup>Department of Speech and Language Pathology, Faculty of Education and Rehabilitation Sciences, University of Zagreb, Zagreb, Croatia
- <sup>54</sup>Department of Speech–Language Pathology and Rehabilitation Sciences Institute, University of Toronto, Toronto, ON, Canada
- <sup>55</sup>Toronto Rehabilitation Institute, Toronto, ON, Canada
- <sup>56</sup>School of Allied Health, Human Services and Sport, La Trobe University, Melbourne, VIC, Australia
- <sup>57</sup>Centre of Research Excellence in Aphasia Recovery and Rehabilitation, La Trobe University, Melbourne, VIC, Australia
- <sup>58</sup>Institut du Cerveau (Paris Brain Institute), Sorbonne Université, ICM, Inserm, CNRS, AP-HP, Hôpital Salpêtrière, Stroke Unit, DMU Neuroscience 6, Paris, France
- <sup>59</sup>RehaNova Rehabilitation Hospital and Department of Special Education and Rehabilitation, University of Cologne, Cologne, Germany
- <sup>60</sup>Sint Maartenskliniek, Rehabilitation Centre and Centre for Language Studies, Radboud University, Nijmegen, the Netherlands
- <sup>61</sup>Warrington Hospital, Warrington and Halton NHS Foundation Trust, Warrington, UK
- <sup>62</sup>Department of Neurology, Charité Universitätsmedizin Berlin, Berlin, Germany
- <sup>63</sup>UAB Epilepsy Centre, Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA
- <sup>64</sup>Division of Rehabilitation, Ageing and Wellbeing, School of Medicine, University of Nottingham, Nottingham, UK
- <sup>65</sup>Rijndam Rehabilitation, Rotterdam, Rotterdam, the Netherlands
- <sup>66</sup>Department of Rehabilitation Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
- <sup>67</sup>Department of Neurology and Neurosurgery, Erasmus University Medical Center, Rotterdam, the Netherlands
- <sup>68</sup>College of Allied Health Sciences, East Carolina University, Greenville, SC, USA

\*Corresponding author [m.brady@gcu.ac.uk](mailto:m.brady@gcu.ac.uk)

**Background:** People with language problems following stroke (aphasia) benefit from speech and language therapy. Optimising speech and language therapy for aphasia recovery is a research priority.

**Objectives:** The objectives were to explore patterns and predictors of language and communication recovery, optimum speech and language therapy intervention provision, and whether or not effectiveness varies by participant subgroup or language domain.

**Design:** This research comprised a systematic review, a meta-analysis and a network meta-analysis of individual participant data.

**Setting:** Participant data were collected in research and clinical settings.

**Interventions:** The intervention under investigation was speech and language therapy for aphasia after stroke.

**Main outcome measures:** The main outcome measures were absolute changes in language scores from baseline on overall language ability, auditory comprehension, spoken language, reading comprehension, writing and functional communication.

**Data sources and participants:** Electronic databases were systematically searched, including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Linguistic and Language Behavior Abstracts and SpeechBITE (searched from inception to 2015). The results were screened for eligibility, and published and unpublished data sets (randomised controlled trials, non-randomised controlled trials, cohort studies, case series, registries) with at least 10 individual participant data reporting aphasia duration and severity were identified. Existing collaborators and primary researchers named in identified records were invited to contribute electronic data sets. Individual participant data in the public domain were extracted.

**Review methods:** Data on demographics, speech and language therapy interventions, outcomes and quality criteria were independently extracted by two reviewers, or available as individual participant data data sets. Meta-analysis and network meta-analysis were used to generate hypotheses.

**Results:** We retrieved 5928 individual participant data from 174 data sets across 28 countries, comprising 75 electronic (3940 individual participant data), 47 randomised controlled trial (1778 individual participant data) and 91 speech and language therapy intervention (2746 individual participant data) data sets. The median participant age was 63 years (interquartile range 53–72 years). We identified 53 unavailable, but potentially eligible, randomised controlled trials (46 of these appeared to include speech and language therapy). Relevant individual participant data were filtered into each analysis. Statistically significant predictors of recovery included age (functional communication, individual participant data: 532,  $n = 14$  randomised controlled trials) and sex (overall language ability, individual participant data: 482,  $n = 11$  randomised controlled trials; functional communication, individual participant data: 532,  $n = 14$  randomised controlled trials). Older age and being a longer time since aphasia onset predicted poorer recovery. A negative relationship between baseline severity score and change from baseline ( $p < 0.0001$ ) may reflect the reduced improvement possible from high baseline scores. The frequency, duration, intensity and dosage of speech and language therapy were variously associated with auditory comprehension, naming and functional communication recovery. There were insufficient data to examine spontaneous recovery. The greatest overall gains in language ability [14.95 points (95% confidence interval 8.7 to 21.2 points) on the Western Aphasia Battery-Aphasia Quotient] and functional communication [0.78 points (95% confidence interval 0.48 to 1.1 points) on the Aachen Aphasia Test-Spontaneous Communication] were associated with receiving speech and language therapy 4 to 5 days weekly; for auditory comprehension [5.86 points (95% confidence interval 1.6 to 10.0 points) on the Aachen Aphasia Test-Token Test], the greatest gains were associated with receiving speech and language therapy 3 to 4 days weekly. The greatest overall gains in language ability [15.9 points (95% confidence interval 8.0 to 23.6 points) on the Western Aphasia Battery-Aphasia Quotient] and functional communication [0.77 points (95% confidence interval 0.36 to 1.2 points) on the Aachen Aphasia Test-Spontaneous Communication] were associated with speech and language therapy participation from 2 to 4 (and more than 9) hours weekly, whereas the highest auditory comprehension gains [7.3 points (95% confidence interval 4.1 to 10.5 points) on the Aachen Aphasia Test-Token Test] were associated with speech and language therapy participation in excess of 9 hours weekly (with similar gains notes for 4 hours weekly). While clinically similar gains were made alongside different speech and language therapy intensities, the greatest overall gains in language ability [18.37 points (95% confidence interval 10.58 to 26.16 points) on the Western Aphasia Battery-Aphasia Quotient] and auditory comprehension [5.23 points (95% confidence interval 1.51 to 8.95 points) on the Aachen Aphasia Test-Token Test] were associated with 20–50 hours of speech and language therapy. Network meta-analyses on naming and the duration of speech and language therapy interventions across language outcomes were unstable. Relative variance was acceptable ( $< 30\%$ ). Subgroups may benefit from specific interventions.

**Limitations:** Data sets were graded as being at a low risk of bias but were predominantly based on highly selected research participants, assessments and interventions, thereby limiting generalisability.

**Conclusions:** Frequency, intensity and dosage were associated with language gains from baseline, but varied by domain and subgroup.

**Future work:** These exploratory findings require confirmatory study designs to test the hypotheses generated and to develop more tailored speech and language therapy interventions.

**Study registration:** This study is registered as PROSPERO CRD42018110947.

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# List of supplementary material

**Report Supplementary Material 1** Overview of each data set in the RELEASE study database

**Report Supplementary Material 2** Unavailable potentially eligible data sets and individual participant data

**Report Supplementary Material 3** Additional figures for *Chapter 4*

**Report Supplementary Material 4** Additional figures for *Chapter 5*

**Report Supplementary Material 5** Speech and language therapy frequency and goodness of fit to baseline, sex, age and time; model by language domain

**Report Supplementary Material 6** Speech and language therapy duration and goodness of fit to model by language domain

**Report Supplementary Material 7** Speech and language therapy intensity and goodness of fit to baseline, sex, age, time since index stroke; model by language domain

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**Report Supplementary Material 9** Speech and language therapy home practice tasks and goodness of fit to model by language domain

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**Report Supplementary Material 16** Speech and language therapy functional relevance of speech and language therapy and goodness of fit to model by language domain

**Report Supplementary Material 17** Speech and language therapy level of difficulty and goodness of fit to model by language domain

**Report Supplementary Material 18** Duplicate data, choice of data items and justification

Supplementary material can be found on the NIHR Journals Library report page (<https://doi.org/10.3310/RTLH7522>).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

# Glossary

**Anchor measure** The measurement instrument (scale) used by the most primary research data sets for each language domain. The identified anchor measure was the scale to which all other scales (minority measures see *Domains of Language*) were transformed to support meta-analysis and clinical interpretation of the findings.

**Aphasia** An acquired neurological impairment that affects a person's ability to participate in any activity that depends on language (i.e. activities that involve understanding what is heard, producing language when speaking, reading or writing).

**Auditory comprehension** The ability to understand the meaning of a spoken word (or sequence of words).

**Co-interventions** Pharmacological, brain stimulation or other interventions that may be offered alongside, or as an alternative to, speech and language therapy, with the aim of improving a person's language or communication abilities, activities or participation.

**Conventional speech and language therapy** An umbrella term for a speech and language therapy intervention that is delivered but not described beyond a generic label (e.g. therapy that was conventional, traditional, standard, typical, as directed by the therapist, usual).

**Domains of language** The different modalities or categories of the ways in which we use language. Changes in language abilities are typically measured within these modalities. For the REhabilitation and recovery of peopLE with Aphasia after StrokE study, these were prespecified as overall ability (or, conversely, severity of language impairment), auditory comprehension, spoken-language production (reported as naming and other spoken language), reading comprehension, writing and functional communication.

**Dosage of intervention** The total number of hours for which a defined speech and language therapy intervention was provided.

**Duration of intervention** The total number of weeks over which a defined speech and language therapy intervention was delivered.

**Frequency of intervention** The average number of days each week that a defined speech and language therapy intervention was delivered.

**Functional communication** The ability to communicate in a 'real-world' functionally relevant situation. Typically, functional communication considers 'real-world' communication with another person, with the opportunity in a face-to-face situation of using all forms of communication, such as gestures and facial expression, as well as spoken words. It also reflects the ability to understand the speaking partner's contribution to that interaction.

**Individual participant data** Information about individual people gathered during their involvement in a primary research study, which may include information on their language abilities, the therapy they received and their recovery over time.

**Intensity of intervention** The number of hours each week that a defined speech and language therapy intervention was delivered.

**Minority measure** Any measurement instrument (scale) used in the primary research studies that contributed to the language domains of interest but was not identified as the anchor measure; data gathered on minority measures were transformed to the scale of the anchor measure to support meta-analysis interpreted in the context of the anchor measure scale.

**Mode of delivery** The way in which a speech and language therapy intervention was delivered (face to face, computer supported or self-managed, one to one or group).

**Overall language ability** A global measure of language abilities that typically includes auditory comprehension, spoken-language production, reading comprehension and writing abilities.

**Reading comprehension** The ability to read written word(s) and assign meaning to them.

**Recovery** Improvement over time on language measurements taken at the start of the study to those taken at subsequent points in time.

**Regimen** The description of therapy in terms of the frequency, intensity, duration and dosage of the intervention.

**Social support and stimulation** The provision of informal encouragement and general opportunities to use language in everyday situations.

**Speech and language therapy** The provision of targeted practice or rehabilitation tasks that aim to improve a person's language or communication abilities, activities or participation.

**Spoken-language production** The ability to communicate a concept to others by speaking a word (e.g. naming an object) or sentences.

**Study entry** The time point of a participant's enrolment in a primary research study, expressed (in the context of the REhabilitation and recovery of peopLE with Aphasia after StrokE study) as the numbers of days since the onset of aphasia.

**Tailoring** The act of customising interventions for individuals by changing the level of task difficulty and/or making them more relevant to the person's everyday communication needs.

**Target of intervention** The aspects of language impairment that an intervention is intended to address [categorised, by consensus, based on the REhabilitation and recovery of peopLE with Aphasia after StrokE study data set as spoken-language speech and language therapy, auditory comprehension speech and language therapy, mixed speech and language therapy (both spoken and auditory comprehension of language are targeted), word-finding speech and language therapy, reading comprehension speech and language therapy and writing speech and language therapy].

**Theoretical approach of intervention** The underlying rationale for the speech and language therapy (categorised, by consensus, based on the REhabilitation and recovery of peopLE with Aphasia after StrokE study data set as functional or pragmatic therapy, phonological therapy, semantic therapy, semantic and phonological therapy, constraint-induced aphasia therapy, melodic intonation therapy, conversational partner-training therapy, verbal therapy and multimodal therapy).

**Transformation** The process by which individual participant data gathered using a minority measure was systematically adjusted using a mathematical operation, on each observation, to the scale of the anchor measure, for each language domain.

**Writing** The ability to communicate through sequencing written symbols (letters) to create words and sequencing of words to create sentences that another person can read and comprehend the intended meaning.

## List of abbreviations

AAT	Aachen Aphasia Test	PICA	Porch Index of Communicative Ability
AAT-SSC	Aachen Aphasia Test-Spontaneous Speech Communication	PLORAS	Predicting Language Outcome and Recovery After Stroke
BNT	Boston Naming Test	PPI	patient and public involvement
CAT	Comprehensive Aphasia Test	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CI	confidence interval	RCT	randomised controlled trial
GCU	Glasgow Caledonian University	RELEASE	REhabilitation and recovery of peopLE with Aphasia after Stroke
GRADE	Grading of Recommendations Assessment, Development and Evaluation	ROBIS	Risk Of Bias In Systematic reviews
ICF	International Classification of Functioning, Disability and Health	SLT	speech and language therapy
ID	identifier	SSNAP	Sentinel Stroke National Audit Programme
IPD	individual participant data	TIDieR	Template for Intervention Description and Replication
IQR	interquartile range	TOM	Therapy Outcome Measure
mRS	modified Rankin Scale	TT	Token Test
NIHR	National Institute for Health and Care Research	TT-AAT	Token Test from the Aachen Aphasia Test
NIHSS	National Institutes of Health Stroke Scale	WAB	Western Aphasia Battery
NMAHP	Nursing, Midwifery and Allied Health Professions	WAB-AQ	Western Aphasia Battery-Aphasia Quotient
OR	odds ratio		



## Plain English summary

Worldwide, > 3.5 million people each year have a stroke that causes aphasia. Aphasia is a language problem that affects speaking, understanding of speech, reading and writing. Speech and language therapy supports aphasia recovery, but therapists need better information about what type of therapy, how often, for how many hours each week and for how long gets the best recovery. We explored how language recovery relates to speech and language therapy, stroke and type of aphasia.

We made a database from 5928 people with aphasia after stroke, in 174 studies across 28 countries. We used information about how each person recovered (or did not recover) following speech and language therapy. We explored the patterns of language recovery, what predicted recovery and what type of therapy was linked to the greatest improvements, for whom and when.

Language recovery was influenced by a stroke survivor's age, their aphasia severity and how long it took to start therapy. Language scores improved for all groups but improved most among people who had speech and language therapy, those aged  $\leq 55$  years, and those who started speech and language therapy soon after their stroke. Improvements lessened as time after stroke increased.

The greatest gains in language, on average, were seen among people who had speech and language therapy 3 to 5 days per week, for 2 to 4 hours each week; understanding of speech improved most with speech and language therapy for > 9 hours over 3 or 4 days per week. Improvements were greatest when 20–50 hours of therapy were delivered. Specific approaches to therapy may suit some people more than others. We need to investigate how best to adapt speech and language therapy to suit a person's age and sex, the severity of their aphasia and how long it has been since their stroke. Speech and language therapy that was relevant to patients' needs was associated with the best gains.



# Scientific summary

## Background

Aphasia (impairment of language) is a common and devastating long-term consequence of stroke. Its impact extends beyond the language domains of spoken language, auditory comprehension, reading comprehension and writing. Stroke survivors with aphasia experience poorer functional recovery (with comprehension deficits in particular affecting activities of daily living), continence and emotional well-being after stroke, than stroke survivors with intact language abilities. People with aphasia are also less likely to return to work or even return home.

Speech and language therapy benefits people with stroke-related aphasia. Maximising language recovery is a research priority for stroke survivors, carers and health-care professionals. We need greater insight into the contribution to recovery across language domains made by individual characteristics (e.g. age, stroke and aphasia profiles) and by the components of speech and language therapy (target and theoretical approach, delivery model and regimen).

## Objectives

We aimed to explore:

- the pattern of language recovery following stroke-related aphasia
- the predictors of language recovery outcomes following aphasia
- the components of effective aphasia rehabilitation interventions
- whether or not some interventions (or intervention components) were more beneficial for some subgroups (individual, stroke or aphasia characteristics) than others.

## Methods

We created an international aphasia database that included individual participant data on demographics, stroke profiles, language impairment, and speech and language therapy interventions and subsequent outcomes across a range of language domains. The database (Integrated Research Application System number 179505) met existing data-sharing guidelines and followed a prespecified protocol (PROSPERO CRD42018110947). Our reporting observes the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and relevant extensions. We employed Guidance for Reporting Involvement of Patients and the Public and referred to the grading quality of evidence and strength of recommendations [using the Grading of Recommendations Assessment, Development and Evaluation and the Risk Of Bias In Systematic reviews (ROBIS) tools] to support judgements of the impact of the quality of the evidence on our findings.

We systematically searched the following databases (from inception to September 2015) using a randomised controlled trial-optimised search strategy: Cochrane Stroke Group Trials Register, Cochrane Central Register of Controlled Trials and other Cochrane Library databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment Database), MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine Database, Linguistic and Language Behavior Abstracts and SpeechBITE. We imposed no language restrictions. We searched for data sets containing anonymised individual participant data on at least 10 people with aphasia following stroke (collected with ethics approval), including measures of language impairment and time since stroke.

The identified records were screened for eligibility. Full-text reports were reviewed by two independent researchers; disagreements were resolved through discussion with a third researcher when necessary. Randomised controlled trial, non-randomised controlled trial, cohort, case series and registry data sets were included. Primary researchers of identified records were invited to contribute electronic data sets. Eligible data sets in the public domain were also identified and transcribed. We developed and piloted a data extraction table, which supported retrieval of demographic, environmental, stroke and language data at individual participant data level, as well as descriptors at study level, including quality criteria (selection, detection and attrition bias). Speech and language therapy interventions from identified studies described targeted rehabilitation tasks that sought to enhance language abilities, activities or participation. These interventions were extracted using the Template for Intervention Description and Replication, and additionally categorised by impairment target and theoretical approach. Data extraction was rigorously checked by a second researcher. When possible, we confirmed data extraction with the primary researchers. Ensuring data integrity was essential to the project.

We converted all data sets into SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA). Prior to analysis, we cleaned all data relating to prespecified variables required for our planned analyses. Across data sets, language abilities were captured on a range of different assessment tools (sometimes in various language adaptations). Language or version variations were treated as separate tools. For each domain, we identified the assessments used; calculated the median score, interquartile range, minimum and maximum; and identified an anchor measure for that domain (the measurement used by the most data sets). All other measures for that domain (minority measures) were transformed to match the format, distribution and range of each anchor measure, using a prespecified algorithm.

Our project aimed to generate hypotheses and to highlight important avenues for further research. We therefore did not employ a strict experimental, hypothesis-testing approach, but, instead, used statistical inferencing to inform the description of participant populations, data items and research questions for future large-scale definitive experimental investigations. We conducted one-stage, random-effects meta-analyses and network meta-analyses based on our individual participant data database. Analyses comprised individual participant data from both electronic data sets and the public domain; these combined data were filtered for relevance into analysis-specific data sets, which were then analysed using a model that considered the clustering of individual participant data in a study. In this way, we explored the subtleties of a highly heterogeneous group of people with aphasia after stroke, controlled for individual predictors. This supported detailed exploration of the influence of participant-level covariates on speech and language therapy treatment effects across a range of language domains.

## Results

We created a database of 5928 individual participant data on people with aphasia after stroke, gathered from 174 data sets across 28 countries. Half of the data sets were based on an English-speaking population, 27% were randomised controlled trials and 7.5% were unpublished. Our search identified an additional 53 randomised controlled trials (of which 46 appeared to include a speech and language therapy intervention) as potentially eligible for inclusion, but their individual participant data were unavailable. Speech and language therapy interventions were described for half of the included data sets and almost half of the participants. Limited language individual participant data both at baseline and after an intervention restricted the data available for our meta-analyses of speech and language therapy interventions for aphasia.

Interventions were complex and wide-ranging. Classification of speech and language therapy by impairment target and theoretical approach required a consensus method. We considered risk of bias at both primary data set and meta-analysis level. We endeavoured to address any risk of bias methodologically and considered that risk in the interpretation of the findings.

## Patterns of language recovery

A paucity of data on participants who received no speech and language therapy, enrolled within 15 days of stroke onset, and who had not received speech and language therapy in the past precluded analysis of the natural history of recovery or the nature of spontaneous recovery across language domains (individual participant data from one data set). Many participants in our database who were initially allocated to receive no speech and language therapy were permitted to receive speech and language therapy following the study's intervention period. Limited data at the post-intervention time point for those who were allocated to no speech and language therapy precluded effective comparison of the trajectory of language scores over time between those who were allocated to no speech and language therapy and participants who had access to speech and language therapy. Data on those who received only historical speech and language therapy (standard speech and language therapy prior to the research study start) were also limited [22 individual participant data from two randomised controlled trials and 34 individual participant data from three data sets (all study types)], as corresponding post-intervention follow-up values were unavailable or did not meet our minimum eligibility criteria for the analysis.

Among participants who were allocated to receive speech and language therapy, we observed an increase in scores over time. Language impairment scores were higher as time to study entry increased, particularly for measures of overall language ability and naming.

We noted that, across all language domains, the highest absolute proportions of changes in scores were seen in those participants enrolled in a study within 1 month of stroke and in those who were aged < 55 years. This proportion of change appeared to decrease with increasing time since stroke. Although many of these changes since baseline did not appear to be significantly different across different domains (e.g. the 95% confidence intervals overlapped), the estimated median changes in scores were notable from a clinical standpoint for some domains (e.g. 16.7% change on the Western Aphasia Battery-Aphasia Quotient from baseline for overall language ability, 207 individual participant data from 10 randomised controlled trials; 18.9% change in Aachen Aphasia Test-Spontaneous Communication for observer-rated activities, 318 individual participant data from nine randomised controlled trials).

### *Predictors of language recovery*

Baseline language score, age, sex and time since stroke were significantly associated with absolute change in raw language domain scores (overall language ability, 418 individual participant data from 11 randomised controlled trials; auditory comprehension, 508 individual participant data from 17 randomised controlled trials; naming, 346 individual participant data from 14 randomised controlled trials; and functional communication, 608 individual participant data from 16 randomised controlled trials). These variables were included in the base statistical models in subsequent analyses of optimum speech and language therapy interventions. Optimum intervention parameters were identified as those that were associated with the greatest statistically significant mean differences in scores from baseline, which we present as 'peak' or 'highest gains' (or similar terms) in language recovery on these measures.

### *Effective aphasia rehabilitation interventions*

To the base statistical model, we added speech and language therapy regimen (frequency, duration, intensity, dosage), approach (target and theoretical) and delivery (context, mode, expertise, tailoring) variables. The outcome measure of this model was change in absolute raw scores from baseline on the anchor measure, across each language domain. Relative variance was acceptable in these analyses (< 30%).

### **Speech and language therapy frequency (average number of therapy days weekly)**

We observed that the greatest gains in functional communication [0.78 points on the Aachen Aphasia Test-Spontaneous Communication (95% confidence interval 0.48 to 1.09 points), 155 individual

participant data from eight randomised controlled trials] and overall language abilities [14.95 points on the Western Aphasia Battery-Aphasia Quotient (95% confidence interval 8.67 to 21.23 points), 194 individual participant data from six randomised controlled trials] were associated with receiving speech and language therapy 4 or 5 days weekly. Peak gains in auditory comprehension [5.86 points on the Aachen Aphasia Test-Token Test (95% confidence interval 1.64 to 10.01 points), 114 individual participant data from five randomised controlled trials] occurred alongside speech and language therapy delivered 3 or 4 days weekly.

### **Duration (total number of weeks over which speech and language therapy was delivered)**

The duration network geometry was unstable, with small numbers of participants and trials, and fewer connections between nodes; caution should be used when considering these data. We observed that the greatest gains in overall language abilities [17.27 points (95% confidence interval 9.71 to 24.82 points) on the Western Aphasia Battery-Aphasia Quotient, 45 individual participant data from three randomised controlled trials] and auditory comprehension [6.79 points (95% confidence interval 1.69 to 11.88 points) Aachen Aphasia Test-Token Test, 93 individual participant data from five randomised controlled trials] occurred when speech and language therapy was of > 10–20 weeks' duration. The highest naming gains [8.38 points (95% confidence interval 1.24 to 15.51 points) on the Boston Naming Test, 134 individual participant data from three randomised controlled trials] were associated with > 20 weeks of speech and language therapy, and the best functional communication gains [0.8 points (95% confidence interval 0.29 to 1.31 points) on the Aachen Aphasia Test-Spontaneous Speech Communication, 57 individual participant data from two randomised controlled trials] occurred for people receiving speech and language therapy for more than 4 weeks.

### **Intensity (average number of speech and language therapy hours weekly)**

Optimal speech and language therapy intensity varied by language domain. We observed the greatest gains on overall language abilities [15.85 points (95% confidence interval 8.06 to 23.64 points) on the Western Aphasia Battery-Aphasia Quotient, 74 individual participant data from three randomised controlled trials], functional communication [0.77 points (95% confidence interval 0.36 to 1.19 points) on the Aachen Aphasia Test-Spontaneous Speech Communication, 83 individual participant data from four randomised controlled trials] and naming [13.23 points (95% confidence interval 5.83 to 20.64 points) on the Boston Naming Test, 18 individual participant data from two randomised controlled trials] in the context of speech and language therapy for 2 hours weekly. Clinically similar gains were observed alongside 4 and > 9 hours weekly. Naming findings were informed by small numbers of individual participant data and randomised controlled trials, and unstable network geometry, and should thus be treated cautiously. In contrast, the highest auditory comprehension gains [7.30 points (95% confidence interval 4.09 to 10.52 points) on the Aachen Aphasia Test-Token Test, 141 individual participant data from six randomised controlled trials] were associated with > 9 hours of speech and language therapy weekly.

### **Dosage (total number of therapy hours delivered)**

A speech and language therapy dosage of more than 20–50 hours was associated with the greatest gains on overall language ability [18.37 points (95% confidence interval 10.58 to 26.16 points) on the Western Aphasia Battery-Aphasia Quotient, 31 individual participant data from four randomised controlled trials] and auditory comprehension [5.23 points (95% confidence interval 1.51 to 8.95 points) Aachen Aphasia Test-Token Test, 90 individual participant data from seven randomised controlled trials]. The greatest functional communication gains were seen alongside 14–20 hours of speech and language therapy [0.94 points (95% confidence interval 0.34 to 1.55 points) on the Aachen Aphasia Test-Spontaneous Speech Communication] and the greatest naming gains [12.48 points (95% confidence interval 1.34 to 23.63 points) on the Boston Naming Test, 28 individual participant data from two randomised controlled trials] were seen alongside up to 5 hours of speech and language therapy. The numbers of individual participant data and randomised controlled trials, however, were small and the networks unstable in both analyses. In both functional communication and naming, the second-highest

gains were noted to occur alongside 20–50 hours of speech and language therapy [naming: 9.23 points (95% confidence interval 1.75 to 16.7 points) on the Boston Naming Test, 81 individual participant data from five randomised controlled trials; functional communication: 0.77 points (95% confidence interval 0.43 to 1.1 points) on the Aachen Aphasia Test-Spontaneous Speech Communication, 96 individual participant data from nine randomised controlled trials].

The prescription of home practice tasks which augments the speech and language therapy dose contributed to the base model for auditory comprehension scores ( $p = 0.019$ ), as did tailoring of speech and language therapy interventions for functional relevance ( $p = 0.029$ ) and by level of difficulty ( $p = 0.043$ ). Prescribed home practice was associated with the greatest gains in overall language ability [16.69 points (95% confidence interval 10.01 to 23.37 points) on the Western Aphasia Battery-Aphasia Quotient, 87 individual participant data from two randomised controlled trials] and auditory comprehension [5.28 points (95% confidence interval 2.19 to 8.37 points) on the Token Test-Aachen Aphasia Test; 278 individual participant data from seven randomised controlled trials].

Tailoring by functional relevance was associated with the best overall language ability [16.47 points (95% confidence interval 10.95 to 21.99 points) on the Western Aphasia Battery-Aphasia Quotient, 232 individual participant data from six randomised controlled trials], naming [8.79 points (95% confidence interval 1.95 to 15.63 points) on the Token Test-Aachen Aphasia Test, 113 individual participant data from five randomised controlled trials], auditory comprehension [5.26 points (95% confidence interval 2.05 to 8.47 points), 194 individual participant data from seven randomised controlled trials] and functional communication gains [0.74 points (95% confidence interval 0.38 to 1.10 points), 249 individual participant data from six randomised controlled trials]. Tailoring by level of language difficulty was associated with the best gains on auditory comprehension [4.57 points (95% confidence interval 1.55 to 7.60 points), 331 individual participant data from 10 randomised controlled trials]. Notably, adding the speech and language therapy theoretical approach (limited individual participant data), the provider's expertise (professional vs. trained non-professional or family member), the mode of speech and language therapy (face to face, computer based, self-managed) or therapy context (inpatient or outpatient) to the base model made no significant contribution to language outcomes.

### ***Optimal speech and language therapy interventions for subpopulations of people with aphasia***

We explored the impact of speech and language therapy interventions on people with aphasia with respect to their age, time since stroke, aphasia severity, sex and changes in language outcomes from baseline. The data from our subgroup analyses were informed by limited numbers of suitable individual participant data from randomised controlled trial data sets and should be cautiously interpreted in the context of the exploratory nature of this work. Relative variance was modest to low in most analyses.

Across subgroups (and when significant changes from baseline were observed), we noted the highest gains in language performance from baseline occurred among the participants aged < 55 years, female participants and in the context of early (< 3 months since aphasia onset) speech and language therapy intervention.

Both young participants (aged  $\leq 65$  years) and those in the older age group made optimal gains on language outcomes in the context of speech and language therapy interventions of a similar frequency and dosage. Where differences were noted, older participants' language improvements were generally greatest when speech and language therapy regimens were lower in intensity, whereas the younger group had highest language gains alongside more intensive speech and language therapy. Auditory comprehension, however, demonstrated the greatest improvements for both groups along with highly intensive speech and language therapy (of > 9 hours per week).

When speech and language therapy was delivered > 3 months after stroke, optimal gains were observed when therapy was frequent and at a high dosage. The best language gains within 3 months of aphasia onset were associated with less frequent and up to 50 hours of speech and language therapy.

People with mild to moderate aphasia were observed to have the highest change in scores from baseline in the context of speech and language therapy that was at a high intensity (e.g. interventions in excess of 9 hours weekly). However, some of the group's language gains from baseline were non-significant, a finding possibly limited by assessment ceiling effects. For people with moderate to severe aphasia, language gains were highest when associated with speech and language therapy for up to 4 hours weekly over 3–5 days.

Male participants made their greatest language gains in the context of speech and language therapy that was more frequent and intensive than the speech and language therapy interventions associated with female participants' best language gains.

### Strengths

The international, multidisciplinary data sets, obtained in people with aphasia after stroke in clinical and research settings across several language domains, supported rigorous one-stage individual participant data meta-analyses and network meta-analyses and provides important insights into aphasia recovery after stroke. The database included high-quality randomised controlled trials and was developed using rigorous systematic review, data extraction and checking procedures, informed by the primary research teams when possible. We standardised multiple language measures to a single anchor measure for each domain, supporting clinical interpretation of the findings. We extended the Template for Intervention Description and Replication checklist to assist data extraction, synthesis and meta-analyses of complex speech and language therapy rehabilitation interventions. We explored patterns and predictors of recovery, and optimal speech and language therapy interventions for aphasia by language domain and participant subgroup. The findings provide important insights into the understanding of aphasia recovery after stroke.

### Limitations

The exploratory findings require confirmation in definitive research designs. In some cases, the individual participant data database was insufficient to support the planned analysis; therefore, caution should be used when interpreting those data. We observed considerable variation in the collection and reporting of demographic, language and therapy intervention data in the aphasia data sets included. Similarly, reading and writing interventions and outcomes relating to communication participation or activities were rarely available. More than half of the individual participant data were English-language based, with limited individual participant data available in any one other language. Such gaps in the data collection, reporting and evidence syntheses highlight important methodological developments and topics for investigation in future definitive aphasia research.

### Implications for people with aphasia after stroke and for health-care professionals

- We observed an increase in scores over time for participants allocated to receive speech and language therapy, which is probably inclusive of spontaneous recovery alongside early speech and language therapy interventions.
- Given the lack of available natural history data by language domain, distinguishing spontaneous recovery from therapeutic gains may continue to be a challenge. In our data, speech and language therapy access for stroke survivors with long-standing aphasia led to increased scores, supporting therapeutic gains. Nevertheless, clinical interventions are typically delivered in a context of spontaneous recovery. Identifying maximum gains in this context is clinically relevant.

- Language performance at baseline, age and time since stroke were significantly associated with recovery in selected domains.
- Optimal language gains from baseline for people with aphasia after stroke varied by language domain and in response to different levels of speech and language therapy frequency, intensity and dosage.

## Research recommendations

- The data informing the analysis of optimum speech and language therapy interventions for reading and writing were limited. More randomised controlled trials of the effectiveness of speech and language therapy interventions for these language domains are required.
- Data on non-English-speaking populations were severely deficient. Given greater movement of people and languages internationally, more data on aphasia recovery in non-English languages are required.
- Generally, the greatest language improvements were seen in the context of therapy over several days a week, for several hours weekly, for up to 50 hours. Exceptions to this pattern were typically associated with data from a small number of participants, specific subgroups of participants or unstable networks.
- Targeted investigations of dose–response relationships, with specific consideration of subgroups of people with aphasia, are required.
- Development of our understanding of complex rehabilitation interventions in a complex population can be enhanced and methodologically addressed through improvements in research design, data capture, description and reporting, and continued international, multidisciplinary, collaborative initiatives such as the REhabilitation and recovery of peopLE with Aphasia after StroKе study and others supported by the Collaboration of Aphasia Trialists.

## Study registration

This study is registered as PROSPERO CRD42018110947.

## Funding

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# Chapter 1 Background

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## Aphasia

Of the estimated 10.3 million people worldwide who experience a stroke each year, 3.6 million people (35%)<sup>2</sup> are likely to have a stroke-related language impairment known as aphasia. Each year, an estimated 35,000 people in the UK experience a newly acquired aphasia, affecting not only their language abilities (ability to speak, understand, read and write words and sentences), but may also affect their ability to use gesture, tell the time, use money and perform simple mathematical calculations. Of those who experience aphasia, 61% continue to have communication problems 1 year later.<sup>3</sup> Approximately 350,000 people in the UK are thought to be living with aphasia.<sup>4</sup>

## Impact of aphasia

Aphasia is one of the most common and most devastating long-term consequences of stroke<sup>5</sup> and extends beyond the communication domain. Stroke survivors with aphasia have poorer functional recovery ( $p = 0.007$ )<sup>6</sup> {comprehension deficits, in particular, affect activities of daily living [odds ratio (OR) 5.38, 95% confidence interval (CI) 2.35 to 12.34;  $p < 0.001$ ]}<sup>7</sup> continence ( $p = 0.003$ )<sup>8</sup> and emotional well-being ( $r = 0.51$ ;  $p = 0.001$ )<sup>9</sup> after stroke than stroke survivors without aphasia. People with aphasia receive less pain medication than other stroke survivors.<sup>10</sup> Aphasia also negatively affects hospital discharge destination ( $p = 0.002$ ),<sup>6</sup> the likelihood of successful return to work ( $p = 0.009$ )<sup>11</sup> and self-rated health after stroke.<sup>12</sup> These outcomes are despite people with aphasia having more contact with rehabilitation specialists<sup>2</sup> and more rehabilitation interventions<sup>13</sup> (contributing to the higher cost of care for people with aphasia) than those without.<sup>14</sup> In the USA alone, the presence of aphasia at the time of stroke adds US\$2.16B, annually, to the cost of acute stroke care.<sup>15</sup> The communicative quality of those rehabilitation interactions may, thus, benefit from closer investigation.

### *Aphasia and psychosocial impacts*

Aphasia directly influences a person's perception of their own identity<sup>16,17</sup> isolating the person with the communication impairment from their spouse, family and wider social networks.<sup>18,19</sup> Family members have also described feeling isolated.<sup>20</sup> Aphasia intensifies social problems more generally associated with a stroke, restricting or altering social activities.<sup>21</sup> This leads to fewer friendships and smaller social networks than before the stroke, and than both healthy peers and stroke survivors with preserved language abilities.<sup>18,21</sup> With restricted opportunities for social participation, people with aphasia become socially isolated, which severely affects their emotional well-being.<sup>19</sup> Spontaneous recovery of language and communication abilities has been thought to be limited beyond the first year after aphasia onset.<sup>22</sup> Emerging research has questioned this premise,<sup>23</sup> and further evidence indicates that focused therapeutic interventions may provide benefit in later stages after stroke.<sup>24-26</sup>

## Aphasia recovery

### *Aphasia recovery and participant demographics*

Clinical guidelines recommend that people with aphasia are provided with 'realistic recovery prospects' following aphasia,<sup>27</sup> but, based on current evidence, accurate prognosis is difficult. Although age has been associated with language recovery, the nature of that interaction remains unclear.<sup>3,13,28,29</sup> Patient sex has been reported by some to be linked to the incidence of aphasia<sup>13</sup> and initial aphasia profile

(but not recovery<sup>3,28</sup>), although several large, well-controlled studies found no evidence of this effect.<sup>2,3,30</sup> Conducting a large-scale investigation of aphasia after stroke has often required compromise, with language data based on a single item in a global stroke severity scale,<sup>2,3,29</sup> and, in some cases, restricted to one aspect of language use.<sup>3</sup> Details on the ability to speak, understand, read, write and participate in everyday communication activities are often unavailable in these tools, thereby limiting our clinical interpretation of aphasia impact and recovery.

The contribution that socioeconomic status and educational background make to recovery may also be relevant, but the interconnectedness of these factors with cognition and performance on measures of language ability makes this a difficult concept to untangle.<sup>3,31-33</sup> The incidence of aphasia is similar among monolingual and bilingual stroke survivors, although it has been suggested that bilinguals experience a milder aphasia.<sup>34</sup> However, studies using imaging data found that bilinguals' performances on a detailed language assessment protocol were worse than monolinguals' performances.<sup>35</sup> Social support prior to and following a stroke may also positively influence outcome<sup>36,37</sup> and, although opportunities to practise functional language use have been shown to decrease as a consequence of aphasia,<sup>18</sup> they are also an important factor in aphasia recovery<sup>38,39</sup> and research.<sup>38</sup>

### **Aphasia recovery and stroke profile**

Initial stroke severity<sup>13,28</sup> and time since stroke may be important factors in language recovery, the latter specifically in relation to the acceptability of high-intensity therapy.<sup>40,41</sup> There is growing evidence that the site and size of stroke lesion (although perhaps not structural connectivity) are indicators of language recovery.<sup>31,42</sup> Stroke-related problems, including depression and cognition, vision and hearing impairments, are also thought to be important to language recovery and rehabilitation.<sup>43-45</sup> Others suggest that the initial aphasia profile (i.e. severity, domains involved, abilities retained) may predict the pattern of language recovery.<sup>3,28,31</sup> Concomitant stroke-related speech disorders, such as dysarthria (a motor speech disorder) and apraxia (disordered planning of movement to produce speech), may also affect initial functional outcomes and recovery.<sup>46</sup>

## **Speech and language therapy for people with aphasia after stroke**

Effective management and rehabilitation of aphasia is vital.<sup>41</sup> People with aphasia experience significant benefits on measures of functional communication, understanding and spoken language after stroke following speech and language therapy (SLT) than those who do not receive therapy.<sup>41</sup> SLT for people with aphasia is highly complex<sup>47</sup> and typically tailored to a heterogeneous group (*Figure 1*).

Therapy activities may be delivered by a range of therapist-trained providers (therapists, volunteers or family members).<sup>41</sup> There is no indication that individual, group or self-managed therapy delivery approaches using personalised computer software, for example, affect SLT benefits for people with aphasia.<sup>41</sup> Therapy interventions may target a range of language domains (e.g. spoken language, auditory comprehension, writing) or aim to educate carers and staff to maximise communicative effectiveness through conversational support for the person with aphasia. Interventions may adopt any one or more of several theoretical approaches (e.g. melodic intonation or functional, semantic, phonological or multimodal therapy), while the optimum intervention regimen (timing, intensity, frequency, duration and dosage) remains uncertain.<sup>22,41,48,49</sup>

### **Regimen**

Early stroke rehabilitation has been advocated<sup>50</sup> to maximise the period of neuronal reorganisation in the brain subsequent to the stroke lesion,<sup>51</sup> in a context of enhanced rehabilitation environments and stimulation.<sup>52,53</sup> Recent randomised controlled trials (RCTs) of SLT interventions have recruited within clinically relevant timelines (days to weeks after stroke)<sup>54-56</sup> with mixed results, whereas others

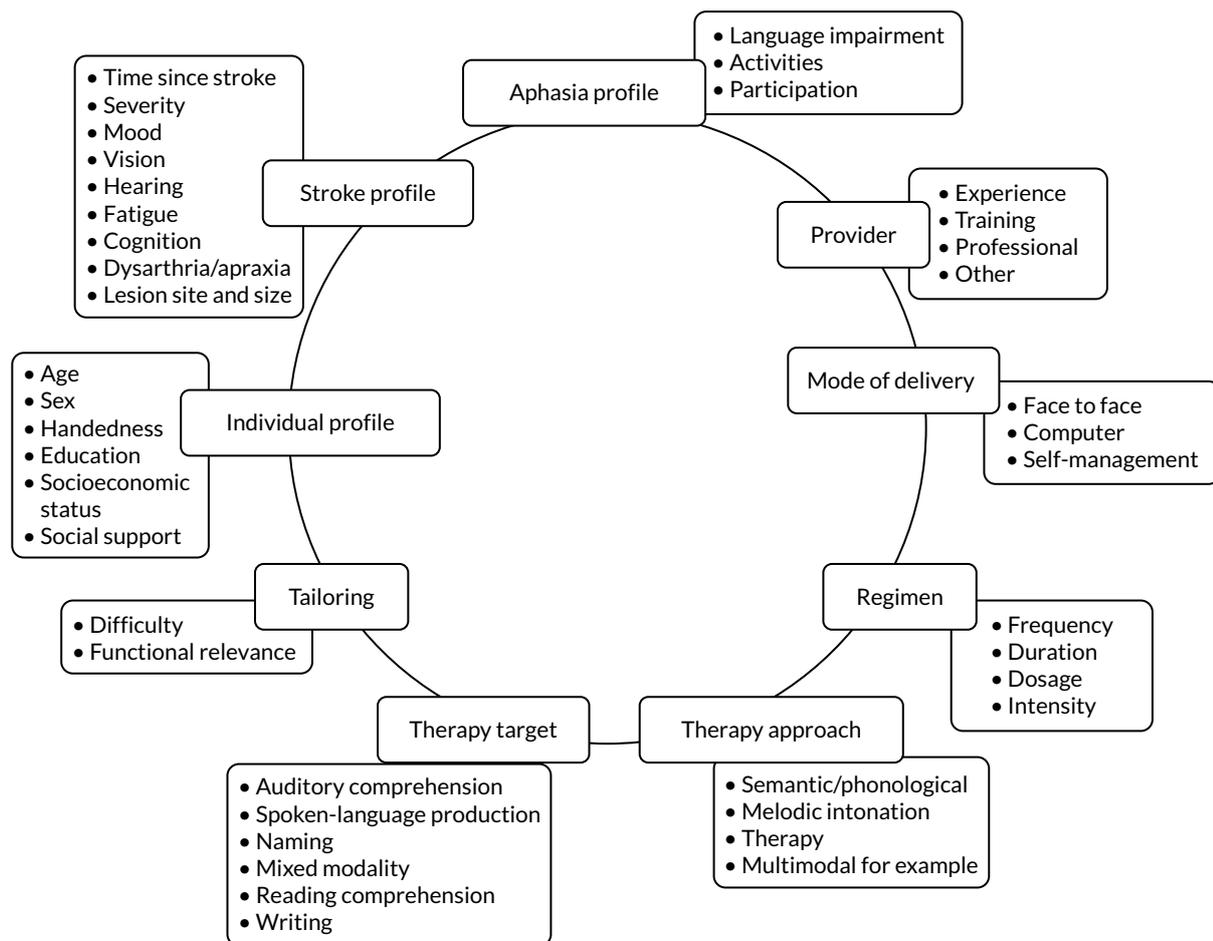


FIGURE 1 Speech and language therapy for aphasia.

have demonstrated benefits among more chronic participants.<sup>57</sup> The optimal timing of language rehabilitation for people with aphasia after stroke continues to be uncertain, and evidence of the most effective SLT intervention regimen, based on therapy frequency (number of therapy sessions weekly), duration (start to end of therapy intervention), intensity (number of hours weekly) or dosage (total hours) provided, is also unclear.

Intensive SLT intervention has been found to benefit functional communication, written language and severity of aphasia, but significantly more people withdrew from (dropouts for any reason  $p = 0.005$ ), or declined to continue with (non-adherence  $p < 0.00001$ ), intensive therapy than less intensive therapy.<sup>41</sup> Interestingly, differential withdrawal and non-adherence rates and the language recovery benefits were observed only among people within 3 months of their stroke. Thus, therapy regimen and participant factors may be important independent and interdependent factors in the effectiveness of and tolerance to SLT for aphasia after stroke.

### Clinical guideline recommendations

UK and international clinical guidelines on aphasia after stroke highlight the paucity of guidance to support therapists' provision of aphasia rehabilitation interventions.<sup>58</sup> Evidence-based stroke clinical guidelines rarely offer specific therapy approach, regimen or mode of delivery recommendations, in contrast to movement rehabilitation recommendations for strength and fitness training, orthoses, electric stimulation and more.<sup>59-61</sup>

Early<sup>62,63</sup> and high-intensity SLT<sup>64</sup> may be effective, but these historic reviews of SLT for aphasia were limited in their design (time-bound, English language only, small number of studies included, summary

data analysis only). The Cochrane review (57 RCTs,  $n = 3002$  participants) found that the potential benefit of high-intensity SLT was confounded by a significantly higher dropout rate from intensive SLT groups.<sup>41</sup> Tailoring to the individual is considered essential,<sup>65</sup> but is based on best practice recommendation. High-quality information from large-scale research projects does not currently exist to guide therapists' choice of an effective therapeutic approach best suited to a specific patient with aphasia (and their families).

Data sets capturing a large number of people with aphasia after stroke are typically based on single-centre data with relatively small numbers of individual participant data (IPD). In studies for which larger numbers of IPD are available ( $n > 200$ ), the quality of information on language outcomes is often restricted, informed by a language data item on a generic stroke scale or screening tool gathered by non-language specialists<sup>2,3,29</sup> and lacking a full description across a range of language skills.

### **Availability of speech and language therapy for people with aphasia**

Information on clinical services for people with aphasia after stroke is difficult to gather. A 2003 UK survey found that therapists providing adult services reported that only one-quarter of their time was spent on aphasia. Of available SLT time for aphasia, just 5% was spent on interventions with an intensity of  $> 3$  hours weekly.<sup>66</sup> Half of SLT time was invested in interventions at an intensity of  $< 3$  hours weekly.<sup>66</sup> An earlier survey reported in 2000 indicated that the average total duration of SLT interventions for people with aphasia ranged from one to five sessions in the UK and Australia.<sup>67</sup> North American SLT interventions ranged from 16 to 20 sessions.<sup>67</sup> Since then, hospital-based SLT in Australia may have increased, with a 2009 survey describing typical intervention intensity of 4 hours weekly (2 hours weekly in acute settings).<sup>68</sup> Information about the SLT received by 278 people with aphasia from across the UK prior to their involvement in the Big Clinical and cost-effectiveness of aphasia computer treatment versus usual stimulation or attention control long term post-stroke (Big CACTUS) trial<sup>69</sup> showed that, in the first 3 months from the index stroke and pre recruitment, participants had received a total dosage of 11 hours of SLT, delivered at an intensity of approximately 1 hour weekly. People who were  $\geq 5$  years after the index stroke received a total dosage of 2.75 hours over the preceding 3-month period, delivered at an intensity of 45 minutes monthly,<sup>69</sup> even lower than the 1 hour weekly reported for people with aphasia in the Australian community.<sup>68</sup>

National audits, although capturing information on access to clinical services, rarely distinguish between time spent with a speech and language therapist for dysphagia (swallowing problems) and aphasia.<sup>2</sup> The Sentinel Stroke National Audit Programme (SSNAP) does, however, highlight the lack of resources for SLT services, a sentiment echoed by therapists.<sup>70</sup> The 2016–17 SSNAP data<sup>71</sup> highlighted stroke specialist services with no speech and language therapist, whereas others had a very limited service (one or less full-time equivalent therapist), leaving service provision for aphasia vulnerable should a therapist be on leave, move post or retire.

There is some suggestion, however, that standard SLT services may be changing in some centres. Usual care provided to participants with aphasia in a recent Australian Phase III trial<sup>72</sup> found that the usual care arm provided early SLT intervention to 81% of participants, compared with just 12% in the Phase II trial.<sup>56</sup> Similarly, the Phase III trial<sup>72</sup> usual care participants received more frequent SLT, and a SLT dosage of 9.5 hours over the first 7 weeks (approximate intensity of 1.5 hours of SLT weekly), compared with an average intensity of 14 minutes of SLT weekly in the Phase II trial.<sup>56</sup> Although the trialists acknowledge that this could be related to the sites simply being part of a trial (the observer effect), it may also suggest a shift in usual SLT interventions over time in those centres.<sup>56,72</sup>

### **Aphasia: a research priority**

Aphasia intervention research was identified twice in the shared top 10 research priorities by stroke survivors, family members and health-care professionals in the 2011 James Lind Alliance Priority

Setting Partnership.<sup>73</sup> Effective aphasia rehabilitation and support interventions for people with aphasia and their families were agreed to be urgent unmet research needs.<sup>73</sup> More recently, the Royal College of Speech and Language Therapists (in the UK) identified aphasia research as a top five research priority topic among their membership.<sup>74</sup> Two further priority-setting initiatives for aphasia research also identified the need for clinically relevant information regarding aphasia therapy intervention approaches, timing, intensity, duration, dose of therapy and therapy provider among the research priorities.<sup>48,49</sup>

## Rehabilitation of aphasia after stroke: a research challenge

The recent priority-setting initiatives have highlighted the gaps in evidence informing the delivery of SLT to people with aphasia. Growing recognition of the importance of focused, early rehabilitation after stroke (for example by Bernhardt *et al.*<sup>75</sup>) has occurred in parallel with increasingly constrained NHS therapy budgets. Prognostic indicators may inform the development of predictive models that acknowledge the existence of parallel spontaneous recovery alongside the benefits of early intervention and brain plasticity.<sup>51</sup> The diversity among people with aphasia and the range of therapeutic interventions have led some to question whether or not large RCTs of SLT for aphasia is the optimal approach to gaining insights into what works best and for whom.<sup>76</sup>

Complex SLT interventions (see *Figure 1*) may be optimised, and specific patient subgroups may benefit from particular SLT interventions. Large-scale investigations of SLT for aphasia are possible and worthwhile.<sup>25,26,55-57,72</sup> International collaboration in this field may be further challenged by the difference in languages across centres and the lack of non-English-language aphasia assessment measures. However, examining the impact of the many permutations of a complex intervention such as SLT on a complex population, which varies by participant, aphasia and stroke profile, would need decades of large, logistically challenging and costly RCTs. Much insight may be gained to inform the design of clinical services and future aphasia research by exploring existing aphasia research data sets.

## Synthesising pre-existing aphasia research data

Data synthesis and secondary analysis of large, aphasia-specific data sets has informed our understanding of SLT for aphasia after stroke. Pooling of group-level summary (aggregated) data demonstrated the effectiveness of SLT for aphasia across language domains. It also identified a possible interaction between the SLT regimen and timing of therapy after stroke, and also methodologically in relation to the choice of attention control interventions.<sup>38,41</sup> Meta-analysis has provided a cost-effective way to inform our understanding of aphasia recovery and rehabilitation before moving forward with costlier RCTs. Such an approach, however, also has limitations.

Traditional meta-analysis makes paired comparisons (therapy A vs. therapy B), but does not easily permit a comparison of therapy A versus B versus C versus D. Clinically, SLT interventions are tailored to individual patients' degrees of language impairment across modalities, attention or levels of fatigue. Group-level summary statistics prevent examination of the influence of participant-level covariates (e.g. age, time since stroke, aphasia severity or sex) on treatment effects.

Secondary analysis of IPD ensures that individuals (their aphasia and stroke profile, recovery and, when relevant, tailored therapy approach) would be analysed in the context of their individual data set, and not aggregated and averaged across a highly heterogeneous group. A collaborative, international approach to data-sharing and retrieval of published and unpublished data sets would support the development of a substantive database to explore key clinical and research questions, such as the patterns and predictors of language recovery, optimum SLT approaches for aphasia rehabilitation and treatment effect modifiers, benefiting researchers, therapists and people with aphasia.

## Aims

The aims were to explore the contribution that individual characteristics (including stroke and aphasia profiles) and intervention components make to the natural history of recovery and rehabilitation of people with aphasia following stroke, and to inform future research design by utilising pre-existing aphasia data to explore the following:

- the natural history of language recovery
- the patient, aphasia, stroke and environmental characteristics that are linked to good language recovery
- the components of effective therapy interventions.

## Research questions

The research questions are in *Box 1*.

### BOX 1 Research questions

- What is the pattern of language recovery following stroke-related aphasia?
  - What is the natural history of language recovery?
  - When is language recovery most likely to occur?
  - Which components of language are most/least likely to recover (overall language ability, spoken language, auditory comprehension, reading comprehension and writing)?
  - Does this vary by language?
- What are the predictors of language recovery outcomes following aphasia in relation to:
  - Aphasia profile (the degree to which overall language ability, auditory comprehension, spoken language, reading comprehension and writing have each been affected in one or more languages)?
  - Individual characteristics (age, education, cognition, mono- or multilingual)?
  - Rehabilitation environment (social support, socioeconomic demographics, ethnicity)?
  - Stroke profile (severity, lesion type, size, location)?
- What are the components of effective aphasia rehabilitation interventions in relation to:
  - Timing of intervention?
  - Frequency, duration, intensity and dose of intervention?
  - Repetition and adherence to home-based therapy tasks?
  - Functional relevance and theoretical approach?
- Are some interventions (or intervention components) more beneficial for some patient subgroups (individual, stroke or aphasia characteristics) than others?

# Chapter 2 Methods

## Overview

We created an international, multilingual database that included IPD on demographics, language impairment, stroke and SLT interventions. The purpose of our database was to support exploration of a range of key clinical questions relating to SLT for aphasia after stroke. The REhabilitation and recovery of peoplE with Aphasia after StrokE (RELEASE) IPD meta-analysis and network meta-analysis study followed a prespecified protocol and identified suitable data sets following a systematic review of the literature (PROSPERO CRD42018110947). We did not employ a strict experimental approach and hypothesis-testing. Instead, we sought to use statistical inferencing to identify promising lines of enquiry for specific investigation in future large-scale definitive experimental investigations in which participant populations and data items could be well defined.

The RELEASE study database (Integrated Research Application System number 179505) (Figure 2) met existing data-sharing guidelines<sup>78</sup> and the International Committee of Medical Journal Editors' proposal,<sup>79</sup> and the reporting observes the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and relevant extensions.<sup>80-85</sup> We employed the Template for Intervention Description and Replication (TIDieR) to support data extraction of the complex SLT interventions,<sup>86</sup> the Guidance for Reporting Involvement of Patients and the Public (GRIPP2)<sup>87</sup> and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to support judgements of the impact of the quality of the evidence on our findings.<sup>88</sup>

## Studies included in the review

### Types of studies

Data sets with IPD on people with aphasia after stroke were sought. We particularly looked for IPD data sets from RCTs, recognising their rigour and robustness for our planned analyses, by using a RCT-optimised search strategy. However, other study designs that met our eligibility criteria were also included, for example non-RCT, cohort and case series studies,<sup>89,90</sup> as well as clinical and research registries (Box 2). Non-RCT designs (including cohort and case series) were included in covariate-adjusted analyses of recovery profiles and predictors of prognosis after stroke.<sup>89,91</sup> We applied no restrictions to study design, data set age, country, minimum number of time points, duration of follow-up, language of data collection or publication.

### Types of study designs included

The primary research studies included in the RELEASE study were categorised according to study design:

- RCTs – participants were randomly allocated to study groups that typically differed in the intervention received [or received a control (or no) intervention].
- Non-RCT studies – participants were recruited but random allocation was not applied to group selection by the primary research team.
- Cohort/case series – data sets from a single participant group that did not compare different SLT interventions.
- Registries – clinical or research databases holding information (e.g. demographic, stroke, aphasia and SLT intervention details) on people with aphasia after stroke, which was not directly gathered to address a single research question.

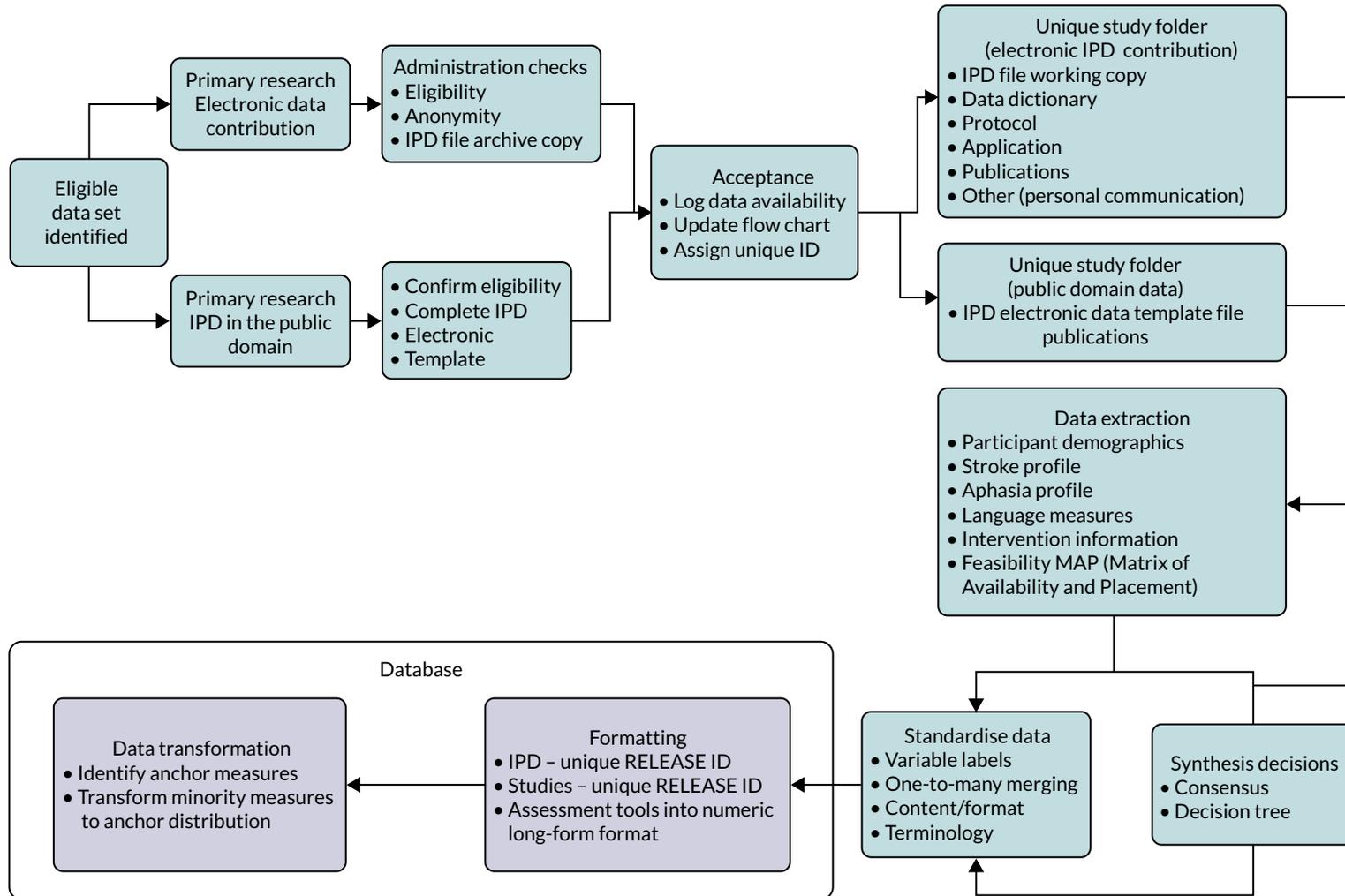


FIGURE 2 Creation of the RELEASE study database. ID, identification.

## BOX 2 Data set inclusion and exclusion criteria

**Data set inclusion criteria**

We accepted data sets that contained anonymised IPD:

- collected as part of an ethically approved primary research study or clinical or research register
- on a minimum of 10 individual participants with aphasia because of stroke
- on aphasia severity
- on time since stroke (or time since aphasia onset) at the time of initial assessment
- relating to formal measures of functional language use, language expression, auditory comprehension, reading or writing.

**Data set exclusion criteria**

Data sets were excluded if they were:

- qualitative data only
- non-language data only (e.g. response times)
- presenting group summary level data only.

***Interventional or non-interventional***

Studies were also classified according to whether they were (1) interventional, whereby SLT was provided in the context of the study, or (2) non-interventional, whereby no SLT was provided in the context of the study.

***Crossover data sets***

We identified crossover data sets (crossover RCTs or non-RCTs) and carefully extracted all data up to the point of crossing over.

**Types of participants**

We screened all participants for inclusion in the RELEASE study database and subsequent analyses. We had no exclusion criteria relating to participants' time since stroke, age, language impairment or access to SLT. If aphasia was not the result of a stroke, those participants' data were excluded and the remaining IPD from that data set (when all other eligibility criteria were met) were included. We defined three participant subgroups relevant to our analysis:

1. Natural history subgroup – participants recruited within 15 days of first stroke and allocated to receive no SLT intervention for a defined period of time in the primary research study. These participants were unlikely to have received significant historical language rehabilitation or SLT.
2. Historical SLT subgroup – participants allocated to receive no SLT intervention in a primary research study, but recruited beyond 15 days of stroke onset. Given the context of aphasia research activity, we assumed that these participants had some clinical access to SLT for their aphasia prior to their study entry.
3. SLT subgroup – participants allocated to receive SLT in the context of a primary research study (research SLT) or permitted continued access to standard SLT during the study period and recruited any time after onset of aphasia.

**Speech and language therapy interventions**

Speech and language therapy was defined as 'any targeted practice or rehabilitation tasks that aimed to improve language or communication abilities, activities, or participation.'<sup>41</sup> When relevant, we sought

primary research studies that included a description of a SLT intervention (*Table 1*) to inform our research questions. Although therapy was typically delivered by a speech and language therapist (a protected professional title in the UK), we also included other therapy providers, as this was one aspect of our planned analysis.

Speech and language therapy interventions were summarised to support clinically meaningful data synthesis and meta-analyses. Narrative descriptions of the SLT approaches, materials and procedures employed were initially extracted as direct quotations (when possible) from published reports.

TABLE 1 Speech and language therapy impairment and theoretical approach categories

Type of SLT	Description
<b>Therapy approach defined by treatment target</b>	
1. Mixed SLT	Targets both auditory comprehension and spoken-language impairments
2. Spoken-language SLT	Targets rehabilitation of spoken language
3. Auditory comprehension SLT	Targets rehabilitation of auditory comprehension
4. Word-finding SLT	Targets rehabilitation of word retrieval or naming
5. Reading comprehension SLT	Targets rehabilitation of reading comprehension
6. Writing SLT	Targets rehabilitation of written language
<b>Therapy approach defined by theoretical approach</b>	
7. Functional or pragmatic SLT	Targets improvement in communication activities and tasks considered useful in day-to-day functioning and often involves targeted practice in real-world communication situations
8. Phonological SLT	Uses phonological approaches and seeks to improve the sound structure of language by targeting improvements in phonological input and output routes
9. Semantic SLT	Uses semantic approaches that focus on interpretation of language, with the aim of improving semantic processing
10. Semantic and phonological SLT	Employs a treatment programme that uses both semantic and phonological approaches
11. Constraint-induced aphasia therapy	Participants are required to use spoken communication alone. Other communicative methods such as gesture may be discouraged
12. Melodic intonation therapy	Employs rhythm and formulaic language to support recovery of language and exaggerated melodic sentence patterns to elicit spontaneous speech
13. Conversational partner-training SLT	Targets communication interaction between the person with aphasia and their conversation partner(s). Conversational partners may be spouse, family member, friends or health-care professionals
14. Verbal therapy	Seeks to improve verbal communication through tasks that include auditory comprehension, spoken language, repetition, naming, sentence construction, semantic or phonological judgements, reading or writing, but do not include music, singing, drawing or gesture-cueing tasks
15. Multimodal therapy	Therapy tasks as listed for verbal therapy (auditory comprehension, spoken language, repetition, naming, sentence construction, semantic or phonological judgements, reading or writing), but that include music, singing, drawing or gesture, with the aim of improving (1) verbal communication (multimodal verbal), whereby non-verbal modalities are employed to facilitate or augment language rehabilitation or (2) total communication (multimodal total), whereby non-verbal modalities are a method of communication

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Descriptions were then tabulated and similar approaches were grouped by an experienced speech and language therapist. These narrative descriptions and preliminary groupings were shared among the collaborators for review and discussion. Following discussion and consensus, we identified 15 possible SLT approaches categorised from two perspectives:

1. the impairment target, for example rehabilitation of spoken language
2. the theoretical approach, for example semantic therapy.

Categories were not mutually exclusive, that is one SLT intervention could include more than one component, and thus be profiled across several categories.

### ***Social support and stimulation of communication***

Social support and stimulation interventions provided informal support and functional language stimulation to the person with aphasia, but did not include targeted therapeutic interventions that aimed to resolve participants' speech and language impairments. Historically they have been used as an attention control in trials of SLT for aphasia or as an adjunct to SLT providing an opportunity to apply new learning in functionally relevant communicative situations.

### ***Conventional speech and language therapy***

Interventions described as 'conventional', 'traditional', 'standard', 'typical', 'as directed by the therapist' or 'usual' SLT (and for which absence of detail prevented more specific categorisation) were referred to as 'conventional SLT'. Such interventions were often delivered in a comparative group or clinical registry. We recognise that conventional therapy in one context may not be comparable with another.

### ***Speech and language therapy co-interventions***

We did not explore the impact of pharmacological or neurostimulation (e.g. magnetic or electrical stimulation such as transcranial direct-current stimulation) co-interventions, which are not typically within the remit of therapists in the UK. Examining the contribution of these co-interventions to language recovery among people with aphasia was beyond the scope and remit of the RELEASE study. We extracted information about the presence of such co-interventions and the timing of delivery and noted this in the data analysis.

## **Types of outcome measures**

Improved ability to use language in real-world situations is the primary goal for aphasia rehabilitation and research. People with aphasia and their family members prioritise functional language use [linked to the International Classification of Functioning, Disability and Health (ICF) components of activity and participation], alongside improvements in language ability (body function).<sup>93</sup> Meta-analysis of functional communication measures is methodologically challenging, as they may be self-reports or proxy reports using rating scales, profiles or questionnaires. Discourse analysis, which observes the use of communication features within a sample of functional language, offers yet another approach, and debate continues about its usefulness and rigour.<sup>94,95</sup> In trials of aphasia rehabilitation, measurement of 'real-world' language use and functional communication is uncommon,<sup>41</sup> and inconsistently captured across studies.<sup>93</sup> Measures of language impairment are considerably more common,<sup>41,96</sup> and reflect overall language abilities (or aphasia severity) across several subtests, which typically include auditory comprehension, spoken language, reading, writing and functional language use.

### ***Main outcome***

The main outcome was change from baseline to follow-up in language performance (language recovery) on formal measures of language ability across six prespecified domains (overall language ability, auditory comprehension, spoken-language production, reading comprehension, writing and functional communication) (Box 3).

## BOX 3 Data extraction items

**Participant characteristics**

- Demographic information (age, sex, handedness, education, cognition, dysarthria, apraxia, languages spoken, depression, other neurological diagnosis, vision and hearing abilities, ethnicity).
- Environmental descriptors (living environment, social support, socioeconomic status).
- Stroke characteristics (hemisphere, type, time since stroke, severity, first or subsequent stroke).

**Language measures**

- Overall language ability.
- Auditory comprehension.
- Spoken-language production.
- Reading.
- Writing.
- Functional communication.

**Study-level information**

- Design.
- Inclusion/exclusion criteria (e.g. dementia, prior stroke).
- Recruitment dates (or publication).
- Number of participants.
- Country and language of data collection.
- Data collection time point(s).
- Blinding.
- Dropouts.
- Randomisation (RCTs only).
- Concealment of allocation (RCTs only).

**Speech and language therapy intervention (when relevant)**

- Who: provider.
- How: delivery mechanism(s).
- Where: context of intervention.
- How much: duration (total number of weeks over which therapy was delivered).
- How much: intensity (hours of therapy provided on a weekly basis).
- How much: frequency (how many days therapy was provided on a weekly basis).
- How much: dosage (total number of hours of therapy provided, home-based practice tasks).
- Tailoring: by difficulty, by functional relevance.
- How well: adherence (data capture and actual adherence rates).
- What: theoretical approach.
- What: treatment target.

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Given the multinational and multidisciplinary nature of this study, we did not predefine a list of all relevant language assessments and language versions of those measures. Instead, we established eligibility criteria that included any language assessment that (1) captured an outcome of relevance to this study, (2) was published and (3) met with the approval of the RELEASE study collaborators. Agreement was achieved on all measures included and their alignment with specific language domains. We excluded screening tools owing to their variable psychometric properties and lack of sensitivity (due to ceiling effects), and the subsequent impact that this would have on our analysis.<sup>97</sup>

### **Data collection time points**

We extracted data on participants at recruitment or entry to the primary research study and at all available time points following this. When follow-up data were available, the time of follow-up was recorded in a continuous fashion in days since primary study baseline. When time to follow-up was given in a category (e.g. 3–6 months), the mean of this time span was taken (i.e. 4.5 months in this example) and converted to days.

## **Identification of data sets for inclusion**

### **Electronic search methods**

We searched the following databases from inception to September 2015 using a RCT-optimised search strategy: Cochrane Stroke Group Trials Register, Cochrane Central Register of Controlled Trials and other Cochrane Library databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment Database), MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine Database, Linguistic and Language Behavior Abstracts and SpeechBITE (see *Appendix 1*). We also reviewed all studies included in and excluded from a 2016 systematic review.<sup>41</sup> We imposed no language restrictions.

### **Study records**

All study records identified in the searches were screened for eligibility for inclusion. When references described potentially eligible data sets, we invited the primary research teams to confirm eligibility and (where appropriate) to contribute their IPD data sets to our RELEASE study database. We also extended an invitation to contribute through our pre-existing networks, including the Collaboration of Aphasia Trialists [[www.aphasiatrials.org](http://www.aphasiatrials.org) (accessed 5 June 2020)].

### **Selection of studies**

One researcher (LRW or KVB) screened titles and abstracts of the records identified using the methods described above and applied the inclusion criteria. Obviously irrelevant titles or reports were excluded. Full-text copies of all the remaining data set reports were reviewed by an independent researcher (KVB, LRW or MCB). Eligibility criteria were ascertained through review of published reports for each study. When published reports were unavailable (for recently completed studies, clinical registries or similar), we clarified eligibility through discussion with the primary research team. Any disagreements about eligibility were resolved through discussion with a third reviewer.

## **Data collection**

For all potentially eligible records identified, we used a systematic approach, starting with an e-mail to the corresponding author describing the aims and objectives of the RELEASE study, enquiring about the potential eligibility of their data set, inviting them to confirm the data set's eligibility and to contribute the anonymised electronic data set. If there was no response, a second approach was attempted 1 month later. When e-mail addresses were invalid, or when there was no response to the second approach, we attempted contact with other members of the authorship team. If these attempts went unanswered, we recorded this as 'no response'. All unavailable data sets and associated IPD were recorded.

We recorded all communications with primary research teams, including queries around eligibility, invitations to contribute and other correspondence. If the primary research team expressed an interest in contributing, we invited them to submit a copy of their anonymised electronic data set in an encrypted format through the Collaboration of Aphasia Trialists' website [www.aphasiatrials.org (accessed 5 June 2020)]. We requested that all electronic data set contributions were accompanied by a data dictionary, a funder report or other reporting of that data set and findings if available. Evidence of gatekeeper (data controller) approval to share the data set with the RELEASE study collaborators and ethics approval for primary research studies were required. When the primary research team required additional permissions to share the data set for the purposes of secondary data analysis, we requested a copy. We also identified eligible IPD data sets in the public domain and extracted the relevant data for inclusion.

### Data extraction

We developed and piloted a data extraction table to support systematic retrieval of data. The data items were identified with reference to our research questions and best practice in reporting of complex interventions and meta-analyses.<sup>82,84–86</sup> (see Box 3). Information sources included published reports and communication with the primary research team to gather data that were otherwise unavailable. When possible, we confirmed data extraction with the primary research team for accuracy and completeness. Following the query resolution process, data items unreported or unavailable from other data sources were recorded as unreported. Items not relevant to that data set were marked as not applicable. For all data sets, a second researcher (MCB) double-checked the data extraction. Disagreements were resolved through discussion or the involvement of a third data extractor.

### Risk of bias in included studies

We extracted information on the quality of each data set using both Cochrane quality items relating to RCTs<sup>98</sup> and the data items from the Joanna Briggs Institute critical appraisal checklists for case-control studies, case series, cohort studies, non-RCTs (quasi-experimental studies) and analytical cross-sectional studies.<sup>99</sup> Aspects irrelevant to our analysis were not extracted; details of the statistical analysis processes applied in the primary research were not relevant to the RELEASE study as we were working with the IPD and not summary statistics; information about exposure to the cause was irrelevant, as aphasia following stroke was a RELEASE study entry criterion; and criteria for the outcome measures used were prespecified for the RELEASE study. Similarly, items relating to data interpretation (e.g. strategies to deal with confounders) were not extracted and synthesised, as these activities reflected on the reporting of the primary research data set and not on the IPD contributed to the RELEASE study database or the planned analysis.

We considered the methodological quality of each included data set in terms of the following potential sources of bias:

- Selection bias – using reported data, we checked whether or not there was any risk of bias in the allocation of individual participants to a specific group in an included trial. In the context of RCTs, for example, we considered whether or not the randomisation sequence generated was truly random and whether or not the sequence allocation was concealed up to the time the individual was allocated to a group. In non-RCT group comparison data sets, we considered whether or not it may have been possible to randomly allocate participants across the groups.
- Performance bias – we documented any co-interventions delivered and whether or not there was any difference between RCT or non-RCT studies. Blinding participants to the delivery of SLT (or not) is almost impossible, although we did seek any examples of when it may have occurred (e.g. computer-based language stimulation vs. a non-verbal cognitive task).

- Detection bias – for all data sets with data collection at baseline and at a post-SLT intervention (or comparison group) follow-up time point, we extracted data on whether or not outcome assessors were blinded to the group, time since onset or other key information.
- Attrition bias – we examined whether or not there was evidence of a systematic difference between comparison groups in the number of dropouts (withdrawals for any reason) or number of non-adherents (those who decline to continue participation during the intervention) after study entry.
- Other biases – we considered other possible sources of bias, such as the similarity of comparison group at baseline, the primary study's relevance to our research questions and outcome reporting bias, when outcomes collected were unavailable and did not contribute to the data synthesis.

For all possible risks of bias, we coded the studies as being at a low, unclear or high risk of bias. We also considered the impact of any potential biases on the findings using sensitivity analyses or narratively.

## Data management

### *Data encryption and storage*

All data contributed to the RELEASE study database were stored at the Nursing, Midwifery and Allied Health Professions (NMAHP) Research Unit at Glasgow Caledonian University (GCU), UK, according to the university's information systems policy. Original primary research data sets and any additional study data were stored on a secure hard drive [a 1 terabyte IronKey™ Enterprise H300 password-protected and encrypted external hard drive (Kingston Technology Corporation, Fountain Valley, CA, USA)] with centralised management. The hard drive was kept in locked storage in a password-protected room. These data were available as data descriptors on the GCU hard drive, which restricted access to the GCU-based project management team only. The primary research data sets were preserved unmodified. Anonymised, password-protected working copies of these primary research data sets were created and stored on the NMAHP Research Unit's designated portion of the university server. Adjustments to these working data sets did not affect the original primary research data.

### *Security and access*

Primary research IPD data sets, data sets created for this project and analyses data sets were accessed only by the RELEASE study project management team at GCU.<sup>100</sup> Data were not accessible to those outside the project collaboration. The project management team and collaborators governed use of the research data, and participated in data analysis plans, interpretation of the findings and preparation and review of the manuscripts based on the planned analyses. All collaborators had an opportunity to contribute to the planned secondary analyses [which were conducted in SAS® version 2.8 (SAS Institute Inc., Cary, NC, USA)].

### *Data preparation for analysis*

We undertook a rigorous process of preparing the IPD data sets for analysis to ensure that the data were valid, as complete as possible, consistent and uniform.

### *Quality assurance and verification*

Each data set was cross-checked against the primary source, such as published papers, protocols and other outputs. We checked within data sets for duplicate participant data sets. We also identified duplication of participant demographics whereby participants taking part in one study went on to participate in a subsequent study led by the same research team, or were reported across dual publications (e.g. as a study group in one study but a comparison group in another). Duplicate participants were identified through (1) careful review of the supporting literature and study materials across primary research teams, (2) checking demographic data across IPD data sets contributed by the same primary research teams and (3) when possible, correspondence with the primary research team. Duplicate entries and any risk of double-counting participant data were excluded from the analysis. This was achieved by removing duplicate participant data sets from one of the data sets, and removing duplicate demographic data

prior to any overview in which the participant descriptors would be double-counted. Other data were considered on a variable-by-variable and analysis-by-analysis basis.

Variable labels for data sets collected in non-English languages were translated by the contributing primary research teams. We confirmed the accuracy and completeness of translations with contributors. Following data extraction, the representative from each primary research team was sent an overview of the data items and details relating to their contributed data set. They were asked to confirm that the information was accurate and complete.

### *Data cleaning and mapping to unit of analysis*

Data were contributed in a range of different formats such as Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA), SAS and Statistical Product and Service Solutions (SPSS) (formerly Statistical Package for the Social Sciences) [IBM Corporation, Armonk, NY, USA (IBM SPSS Statistics from version 19 onwards) or SPSS Inc., Chicago, IL, USA (version 18 and below)]. In the first instance, we cleaned all data sets to reclassify duplicated variable names, removed blank lines and transposed data into a one row per participant format (short form). We converted all data sets into SAS. Prior to analysis, data relating to prespecified variables needed for the RELEASE study analyses (see Box 3) were cleaned. These variables were decided a priori by the research and analysis team and presented to the wider RELEASE study collaboration for review and comment. We ensured that the variable entry matched an agreed uniform format to inform our planned analyses. For example, time since stroke was recorded in days, months and years across RELEASE data sets; the RELEASE collaboration agreed to record 'time since stroke' in the format of 'days since stroke'. When necessary, entries as years or months after stroke were converted to days. In some cases, the record format was a date entry from which days since stroke could be calculated when date of study entry was considered. For each variable of relevance, the primary research data sets and other data sources (publications, protocols, data dictionary) were searched for that variable or indicative surrogate measures. Decisions on how to synthesise these data into a common nomenclature were based on agreement of the wider collaboration. A decision tree was used to ensure standardisation of variable names and ranges when converting data from the original data sets to the RELEASE study analysis data sets.

For some variables, the relevant data were common to all participants across a data set and not included in the contributed electronic IPD data set. For example, if the primary research entry criteria specified right-handed participants, then all participants in that data set were right-handed, whether or not this was recorded in the submitted electronic data set. Similarly, when a specific intervention was delivered to one randomised group, then (unless otherwise specified) the intervention description was common to all participants in that group. In such cases, we imputed and translated those data using one-to-many merging and in keeping with the agreed format for the RELEASE study analyses.

The collaboration then agreed on standard definitions to describe therapeutic interventions in terms of the theoretical and target approach (see Box 3). These definitions were applied to all intervention studies. In some instances, those participants who were allocated to no SLT were permitted to receive usual care SLT after the study's active intervention period had finished. In these cases, we identified the follow-up times that corresponded to the duration of no SLT and took those observations forward for analysis in the no-SLT group. We also identified cases of usual SLT care, study SLT intervention and the corresponding follow-up time points associated with each. We identified the presence of crossover in treatment and took all measurements up to the point of crossover. These data were identified, cleaned to a standardised format and entered into the analysis data set.

According to the needs of the analysis, data-cleaning processes included examining the data set for validity of contents, such as receipt of all relevant participants' data; matching numbers of IPD transferred with those reported in publications; matching variable names to known published assessments and ascertaining any missing domains of assessment from the original data set; examining the content of fields to ensure that they matched prescribed minimums and maximums for known assessments; ascertaining

any transformations of data that had occurred prior to transfer and resolving such queries [e.g. use of a mix of *t*-scores and raw scores in the Aachen Aphasia Test (AAT) across studies]; examining odd values in a given range (e.g. data sets containing a zero value for assessments when this indicated that no assessment had been conducted); and converted data into a numeric format.

## Data integrity and validation

Ensuring data integrity was essential to the project. We audited the data sets using statistical and database methods to detect anomalies and contradictions. For example, we checked the validity and plausibility of contributed data, specifically ensuring that data entries were within the acceptable ranges of variables and outcome measures used in the primary research. When this was not the case, we cross-checked the data with all study records or publications, and communicated with the primary research teams to confirm extreme outliers or other questionable values.<sup>98</sup> We examined distributions and descriptive statistics to audit contributed data and identified irregularities or inconsistencies that required further clarification. These were manually checked with the source data, the data report (if available) and the SAS file.

We checked for any imbalance at baseline between individuals included in RCT or non-randomised groups. Working with IPD at the study level, we used the Wilcoxon signed-rank test to look for significant between-group differences in baseline characteristics, including age, sex, years in education, handedness, time since stroke onset (days) and aphasia severity. For comparisons of sex and handedness between groups, we used the chi-squared test.

## Measures of treatment effect

We identified language outcome measures and worked with outcome data, transformed to the anchor measure, for each domain (see *Anchor and minority measures* and *Data transformation*). We defined measure of treatment effect as the mean of the absolute change from baseline on transformed measures for each of the domains of interest. Effect sizes were estimated and reported with 95% CIs and significance was set at the 5% threshold throughout.

## Sample size

We prespecified that each analysis would be based on a minimum of two data sets. As our eligibility criteria dictated that each data set would have a minimum of 10 IPD, our minimum sample size was 20 people with aphasia after stroke.

## Data conversion and reformatting data files

Data were converted and stored in SAS version 9.4 format for ease of management.

## Data synthesis

Most SLT interventions were described at the primary research study or group level, and only rarely were aspects of that intervention (e.g. the duration or dosage) reported at IPD level in an electronic data set. SLT intervention data were therefore extracted from narrative descriptions in the primary research protocol, electronic data set, published report or through discussion with the primary research team.

A separate data set was generated for each of the following:

- study description and participant demography
- outcomes describing the domains of interest
- SLT intervention and language rehabilitation (and co-interventions when present).

Each data set contained the unique identifier (ID) for constituent participants. This meant that multiple data sets could be linked using this ID to generate a complete picture of the participant's profile across multiple data sets, and all unique participants could be brought together for each of the planned analyses.

### ***Anchor and minority measures***

We prespecified several language domains or outcomes for analysis in the RELEASE study:

- overall language ability
- auditory comprehension
- spoken-language production (including naming)
- reading comprehension
- writing
- functional communication.

For each of these outcomes, a range of assessments (sometimes in various language adaptations) was used. To synthesise the IPD from across these multiple measures, we first identified the most commonly used measurement for each outcome. We profiled all measures used to capture data on that outcome, the number of studies using that measure and the number of IPD available, and calculated the median score, interquartile range (IQR), minimum and maximum for each measurement tool. Language or version variations were treated as separate tools.

An 'anchor measure' was identified for each language domain (e.g. reading) as the measurement instrument used by the most data sets in the RELEASE study database. When this approach resulted in two possible anchor measures, the assessment that had the greater number of IPD in that language domain was identified as the anchor measure. All other assessment tools measuring the same domain, but which were informed by smaller numbers of data sets, were considered 'minority measures'. Minority measures were then transformed to match the format and range of each anchor measure (one for each language domain) through an adapted version of the method previously used in large-scale data synthesis (see *Appendix 2, Box 4*).

### **Data transformation**

Our transformation process was based on the underlying assumption that the anchor and minority measures for a described outcome were similar.<sup>101</sup> The transformations were based on an investigation of the medians, IQRs, minima and maxima of both the anchor and minority measures according to an algorithm (see *Appendix 2, Box 4*). A linear transformation from each minority measure to the anchor measure was applied to each quartile and repeated for each language outcome. Each threshold in the minority instrument was mapped to the corresponding threshold in the anchor measure. Values in the minority measure that fell within a quadrant were mapped to the anchor measure relative to the distance from the quadrant edges. The formula was repeated for each quadrant. In this way, the clinical relevance of changes in scores on the anchor measure was retained.

Three alternative approaches to transformation (normalising, internal normalising and direct linear) were considered but rejected. Normalising transformations (e.g. van der Waerden<sup>102</sup>) requiring pooled ranks across the measures would not be feasible owing to the differences in the width of the various scales. For both normalising and internal normalising approaches, the clinical meaning of any scores or change

of scores would be lost. Direct linear transformation would retain the anchor measure values and, thus, clinical relevance. However, it would require mapping the distribution of the minority measures to the anchor measures without retaining the distribution of the anchor measure itself and, as the measures are often naturally skewed in different directions, this would affect the interpretability.

For each of our analyses, values were generated first for the anchor measure and then for the minority measures. Checks were performed to assess whether or not the ranges, values and directions of changes observed for each anchor measure were consistently reflected when transforming each minority measure into the anchor measure.

## Meta-synthesis methods

Four research questions were addressed in the context of the RELEASE study, in line with the study objectives (see Box 1). The RELEASE study database supported investigation of (1) the progression of language recovery over time following aphasia after stroke, (2) the individual factors, such as demographic and aphasia profile, that potentially play a role in language recovery over time following aphasia after stroke, (3) the components of effective rehabilitation interventions that best facilitate recovery over time following aphasia after stroke and (4) whether or not certain interventions (or intervention components) are more beneficial for some participant subgroups than others.

### Meta-analysis and network meta-analysis

Meta-analyses of aphasia intervention research already exist and have provided evidence-based review and data synthesis of the clinical effectiveness of SLT for aphasia after stroke (e.g. Brady *et al.*,<sup>41</sup> Robey<sup>63</sup> and Bhogal *et al.*<sup>64</sup>). Methodologically, these meta-analyses are usually based on the data synthesis of aggregate group-level summary data. Large group summary approaches taken by RCTs and meta-analysis of RCTs have limitations, particularly in relation to the risk of ecologic bias; aggregate data generated across a complex participant population, such as people with aphasia, risk concealing the possibility of varying individual response to a complex rehabilitation intervention.<sup>76</sup>

Traditional meta-analysis is limited to direct between-treatment (or control) comparisons and group-level descriptors of interventions and aggregated group data on the treatment effects.<sup>103</sup> A more detailed examination of the effectiveness of a specific therapy component is not possible owing to the variability of complex SLT across data sets. Similarly, such approaches cannot accommodate or control for participant demographics or other factors relevant to recovery.<sup>41</sup> Network meta-analysis approaches, however, allow for an estimate of the difference between two (or more) treatments that are not directly compared. For example, studies comparing A versus B or A versus C (direct comparisons) can be combined to give an estimate of B versus C (indirect comparison).<sup>104</sup>

### Individual participant data network analysis approach

Network meta-analysis can be applied to aphasia intervention research using group-level summary statistics,<sup>38</sup> but this approach does not address the limitations of ecological bias, highlighted in the previous section. Confounding is also a risk. We conducted a network meta-analysis based on a large IPD database, which allowed us to explore the subtleties of a highly heterogeneous group of people with aphasia after stroke, control for individual predictors and support the detailed exploration of the influence of participant-level covariates on SLT treatment effects across a range of language-specific measures.<sup>104</sup> Meta-analyses based on aggregated data are typically unable to examine such interactions. In addition, we were aware of some studies that had recorded valuable information on SLT intervention at IPD level.

### One-stage versus two-stage approach

There are two main approaches to an IPD network meta-analysis: a one- or two-stage approach.<sup>104</sup> Two-stage approaches are very similar to the standard meta-analysis approach, working first with

IPD to centrally generate aggregate data for each contributed data set (rather than using the primary research team's reported summary statistics). These aggregate data could then be meta-analysed with summary statistics from other trials for which only aggregate data were available. This approach can, however, lead to bias in effects, greater heterogeneity and lower power to detect associations between language outcomes and continuous variables.<sup>104</sup> It is also very similar in methodology to existing reviews and meta-analyses of summary data.

In contrast, a one-stage approach would allow all available IPD from across the contributed data sets and IPD retrieved from the public domain, filtered for relevance to each analysis, to be combined into a single model (which considered the clustering of IPD within a study). One benefit of this methodological approach is that it can address confounding by enabling the examination of the impact of several participant and language variables on an intervention effect at the same time.

### **Network meta-analysis**

We performed our one-stage network meta-analysis in SAS, using PROC MIXED, with fixed demographic and treatment effects, and study as a random effect. The variance structure was allowed to be unstructured. Study homogeneity was assessed by examining the variance parameters. Network diagrams for each treatment factor were drawn up. Each comparison within each domain was illustrated by a network graph, and supplemented by a table of the number of available IPD in each RCT and treatment node. We used the graphs to explore the balance of the networks and whether or not all levels in a treatment were compared across and within studies. Each comparison in each domain was illustrated by a network graph, and supplemented by a table of the number of available IPD in each RCT and treatment level. Feasibility was contingent on the number of trials and IPD available.

The populations in each data set were expected to differ, and so a base model of age, sex, time since stroke and baseline score was created for each language domain. We also planned to examine interactions between demographic characteristics and treatments, should sample sizes be sufficient. Given the number of tests likely to be undertaken, we were aware of the high risk of false positives. However, the aim of the RELEASE study exploratory analysis was not to generate definitive answers, but to use inference to suggest priority avenues for future research; therefore, we were more concerned with estimated effect sizes than statistical significance.

### **Primary analysis**

We used RCT data as the gold standard for each planned analysis, with only participants from RCTs included in the primary analyses. Analyses that included data from non-RCTs, cohort/case series studies, observational studies, registries and other study design types (as relevant) followed the primary analysis, to judge whether or not they supported the RCT findings (see *Appendix 3, Figure 26*). When they did not agree, the data were further explored to quantify this difference.

To maintain the independence of subjects, we ensured that IPD did not appear in more than one data set for intervention type comparisons, although they could appear in more than one data set when grouped by language domains (e.g. overall language ability, auditory comprehension, reading) (see *Appendix 3, Figure 26*).

## **Patterns of language recovery**

We examined language recovery among people with aphasia across the prespecified language domains: overall language ability, auditory comprehension, naming, other spoken-language production, reading comprehension, writing and functional communication. Analyses were based initially on RCT data, and then expanded to include all study design types (non-RCT group comparisons, cohort, case series and registry data sets).

Descriptions of the patterns of aphasia recovery were generated using four methods across each language domain. As data availability permitted, we described the:

1. natural history of recovery among participants that had no access to SLT
2. trajectory of language recovery over time among participants by assessing their baseline and follow-up scores
3. distribution of language domain scores for participants at study entry
4. absolute proportion of change in language scores from study entry to first follow-up across all domains.

### ***Natural history of language recovery***

We defined the natural history population as a population for whom no active SLT intervention was present, and for whom there was no history of previous SLT. People who were allocated to the no-SLT group in a study were typically permitted to receive usual care SLT after the intervention period of the study had been completed. Any SLT intervention could have an impact on the post-intervention follow-up measures. Depending on the time since the onset of their aphasia, they may also have had historical SLT prior to entering the study as part of usual care. We therefore implemented the following restrictions when extracting eligible IPD to support the examination of the natural history of aphasia recovery:

1. Allocation to the no SLT group in an intervention study.
2. Enrolment to the study with baseline assessment commencing within 15 days of index stroke, to reduce the possibility of unreported initiation of SLT as part of usual care.
3. No history of prior stroke.
4. When longer-term follow-up measurements were available, we reported on the first post-intervention follow-up only, when applicable, to eliminate all instances of access to SLT as part of usual care SLT after the study intervention period, as identified in our data extraction.

We plotted baseline language domain scores along with corresponding language domain values that were available at first follow-up, to examine the trajectory of the natural history of language recovery over time in those participants who were allocated to no-SLT groups.

### ***Language recovery in the context of speech and language therapy***

We also examined the trajectory of language recovery among participants who had access to SLT; we identified those who had access to SLT either as a study participant (SLT group) or reported (or reasonable grounds to assume) historical access to SLT as part of standard health care prior to study enrolment (historical SLT group). We also identified those who were allocated to the historical SLT group (with enrolment beyond 15 days post stroke to exclude those who were part of the natural history analysis) and assessed whether or not there were sufficient data available at the first follow-up period. We sought to eliminate the impact of any SLT intervention (even usual care) in any follow-up data collection time points.

We described baseline and follow-up scores in all available groups for each language domain, when sufficient data were available. Data were presented as plots of language domain scores over time (relative to study entry) and, when applicable, stratified by SLT, no SLT or historical SLT intervention.

### ***Language recovery: change in language scores from baseline by time since stroke***

We examined the role that time since index stroke and study enrolment played on the proportion of recovery observed for each domain score. The study enrolment period in the primary data set was stratified into the following groupings:

- 0–1 month
- > 1–3 months
- > 3–6 months
- > 6 months following index stroke.

We ascertained whether or not participants were allocated to receive a SLT intervention; when possible, we described the absolute proportion of change observed for SLT versus historical SLT (excluding those who were assessed as part of the natural history analysis). We calculated the proportion of change (%) in each language domain score from baseline to first follow-up and plotted these proportion changes by study enrolment period (as categorised earlier). This was described for the RCT population, and then for all study types. We plotted each language domain separately to visualise the proportion of change observed in each domain at different study entry time points. We opted not to stratify data according to baseline severity stratum in combination with aphasia chronicity, as this would have resulted in very small strata and much wider confidence limits, thus precluding informative analyses. We also accounted for the skewness of data measuring language impairment by opting to present medians and IQRs, rather than means and standard errors of the means.

### ***Distribution of language scores at study entry by time since stroke***

All participants were selected from the total population of people with aphasia after stroke. We identified all data available at study entry for each language domain. This time point was selected as all participants were assessed prior to receiving any study intervention. We then ascertained the time of assessment relative to stroke onset. We plotted all transformed language domain observations available at study entry against time of study entry, relative to stroke onset, for each language domain. We then fitted a regression line to these observations and conducted linear regression analyses to describe whether there was a significant trend towards increased or decreased language domain scores with later time to study entry. We considered whether or not the baseline data reflected the trajectory findings based on participants' language scores over time (see *Chapter 4*). We considered the distribution of language scores at clinically relevant time points (e.g. study entry between 0 and 1000 days since stroke). Finally, we considered whether or not there was any suggestion of selection bias in recruitment to aphasia studies based on participants' language scores over time since stroke.

### **Predictors of language recovery**

Demographic and stroke covariates identified as statistically significant from the patterns of language recovery analysis (see *Appendix 3, Figure 26a*) informed our primary statistical analysis of the predictors of language recovery over time. We considered evidence informing other areas of stroke rehabilitation and common assumptions in the context of aphasia rehabilitation.

Whether or not participants had received SLT in the primary research study (SLT/historical SLT or no SLT) was also included in the analyses (see *Appendix 3, Figure 26b*). Language recovery on a continuous scale was regressed onto the covariates of interest. Initially, each predictor was checked using univariable analysis; covariates significantly associated with the primary outcome at a univariable level (i.e. a  $p$ -value of  $< 0.1$ ) were included in the multivariable regression analysis. Thereafter, covariates were introduced and retained in the final multivariable model only if found to be statistically significant. Each analysis included the study ID as a random covariate, to account for possible variability in the outcome measure between studies.

Participants' stroke profiles, demographic characteristics and living contexts at baseline and follow-up (when available) were explored graphically and using summary statistics by showing means and standard deviations for continuous and count data (or median and IQR if data were skewed), and frequency and percentages for binary and categorical data. Standard statistical tests (e.g. chi-squared tests) were employed to check formally for statistical differences.

### ***Factors associated with language score changes: age, sex and time since stroke***

We performed regression, modelling a trend towards increasing proportion of change, and including age, sex and time since stroke (days) as covariates in this model, to ascertain whether or not there was a relationship between age, sex and time since index stroke on the degree of recovery observed.

### ***Distribution of language scores at study entry: age, sex and living context***

Building on the earlier analyses, we identified all participants' data from across all data sets for the specified language domains at study entry in advance of any study-level intervention. Using the data on time since stroke, we plotted the language scores and explored their distribution across different age groups ( $\leq 55$ , 56–65, 66–75 and  $> 75$  years), sex and living contexts.

### **Optimum approach to speech and language therapy for aphasia**

The demographic and stroke covariates identified as statistically significant in earlier analyses were used to create the baseline model to consider the components of effective rehabilitation interventions for people with aphasia after stroke. Once the model was built, additional SLT variables were examined for impact on the primary outcomes (see *Appendix 3, Figure 26c*). Data were analysed as mixed-effects models, with data set as the random effect. Components of therapy (see *Box 3*) were considered on a continuum and explored for meaningful categories.

### ***Beneficial speech and language therapy approaches to language recovery for participant subgroups***

We explored whether or not some interventions (or intervention components) may be more beneficial for some participant subgroups than others. When demographic/stroke variables were significant to the model, a series of one-stage subset analyses were carried out to explore whether or not certain participant groups responded better to certain therapy interventions (see *Appendix 3, Figure 26d*). We also examined participant clustering within trials, which would allow us to distinguish individual participant-based interactions from any data set-based interactions.<sup>103</sup>

### **Risk of meta-biases**

We considered not only the risk of bias in relation to the primary research data sets (see *Risk of bias in included studies*), but also how bias might be a risk in how we conducted our IPD meta-analyses and network meta-analyses. We used the Risk Of Bias In Systematic reviews (ROBIS) tool framework to structure our deliberations on our approach and possible risk of bias; for consideration of the potential risk of bias in the RELEASE study meta-analysis and network meta-analysis, see *Chapter 8*.<sup>105</sup> Risks of selection bias, publication bias and availability bias were among those considered (detailed in the following sections) by a single researcher, and reviewed and discussed with an independent researcher. Consideration was given to any concerns relating to the specification of study eligibility (risk of selection bias), methods used to identify and select studies (risk of selection bias, publication bias), the methods used to collect data (availability bias) and appraise studies and any concerns with the synthesis and findings of our work.

#### ***Selection bias***

We incorporated a systematic review component as the first stage to building our IPD database and actively invited data set contributions from primary research teams that we had no prior collaboration with. We also identified and extracted IPD reported in the public domain, including the grey literature, from primary research teams with which we had no contact. We considered the possible impact of potentially eligible but unavailable IPD data sets.<sup>106</sup> When relevant, we tested the comparability of groups at baseline.

#### ***Publication bias***

Through our rigorous approach to identification and selection of eligible data sets, we identified IPD that were conducted across a range of languages, unpublished or reported in the grey literature, thus reducing the risk of reporting bias.<sup>107</sup> Where the limited availability of suitable data sets rendered a

funnel plot unfeasible, we examined risk of publication bias by looking at the distribution between sample size and those studies that reported significant findings. It was not possible to look at publication bias in the unpublished registry data sets.

### **Availability bias**

We considered the impact of potentially eligible data sets that were unattainable, unavailable to our study or for which the researchers were uncontactable.

### **Other biases**

We considered the possible risk from other sources of bias, including relevance of the primary research study's objectives. We used the ROBIS tool to consider to what extent the RELEASE study meta-analysis and network meta-analysis were at risk of bias.<sup>105</sup>

## **Missing data**

Not all included data sets had collected (or had available) data on all variables of interest to our analyses. In such situations, the analysis was restricted to the subset of data sets with available data on the variable. However, when primary research materials indicated that a data item was collected but that it was unavailable in the contributed electronic data set, we attempted to extract that data from alternative sources, including:

- retrieving the data from the text descriptions of published manuscripts or reports
- retrieving the data from unpublished materials
- requesting the missing data items from the primary research team.

If, despite our efforts, specific variable data remained unavailable, then that data item was marked unavailable (labelled in the data set as unreported). If a variable had > 20% missing data from the primary research data set, this variable was excluded from the primary analyses.

### **Missing completely at random**

Data were examined for patterns of loss or whether or not the data were missing completely at random by recoding the variable of interest into 'missing' or 'not missing'. This variable was compared with demographic variables that may have had an influence on recording that information (e.g. participants' age, sex, stroke), and then with the other variables available. We used the *t*-test for comparisons of missing data with continuous variables such as age (or the Mann–Whitney *U*-test, depending on the normality of the distribution). When comparisons involved categorical variables, we used the chi-squared test to indicate whether or not the missing data were substantially different from the data reported (not missing). When there was no evidence of an influence, the data were treated as if assumed to be missing completely at random. Data missing at random were excluded from our modelling and analysis.

## **Assessment of heterogeneity**

We considered the degree to which there was any variability in the data sets gathered and synthesised in our analysis in relation to clinical, methodological or statistical heterogeneity. We considered the impact of between-study methodological differences such as study design, randomisation and blinding of outcome measurement in the context of risk of bias (see *Chapter 3*). Between-study differences in the choice of outcome captured or the measurement tool employed were accommodated in the data extraction and synthesis approach, which restricted data extraction to published assessment tools. We sought agreement across our international collaboration on the categorisation of outcome measurement tools

and the transformation of data to an anchor measure. The objectives were to explore the impact of a wide range of SLT interventions, but, for each analysis, we collated, synthesised, analysed and presented the relevant data separately, ensuring that each meta-analysis was homogeneous in terms of participants, therapy and outcomes.<sup>98</sup>

The analysis was not a standard meta-analysis of a series of RCTs in which the treatment effect to be measured was captured using the same tool across all eligible RCTs; thus, the standard assessments of heterogeneity (e.g. the  $I^2$ ) were unsuitable for our meta-analyses purposes and mostly not calculable. Instead, we assessed heterogeneity by examining the relative size of the variability due to study differences to the overall variability in the data. Analyses with > 25% of variability due to data set differences underwent careful examination of the contributing data sets to ensure that no data set was having an undue influence on the findings and that the groupings (e.g. the thresholds for dosage) were reasonable and not highly unbalanced. When a contributing data set did have undue influence or groupings were unbalanced, the thresholds were adjusted. When the relative variability exceeded 50%, then the findings were highlighted as unreliable and were not taken forward or presented.

For the network IPD meta-analysis, we undertook a series of intervention comparisons within and between data sets, also known as direct and indirect comparisons. Direct comparisons would occur in the context of a single data set for which treatment A was compared with treatment B and another data set compared treatment B with treatment C. As previously described, using network meta-analysis allowed us to make comparisons between data sets; thus, we were able to directly compare treatments A and B, B and C and indirectly compare A with C. We made every attempt to ensure that, in developing the networks, we had no orphan interventions (an intervention that appears in only one study and has no direct comparison with any other intervention).

## Sensitivity analyses

We conducted a series of sensitivity analyses to examine the robustness of any data synthesis decisions on the findings.

### Choice of language measurement

We explored the impact of our prespecified choice of assessment tool in situations in which a data set had two or more assessment tools eligible for synthesis in a single language outcome. We considered the impact on findings had the alternative assessment been selected to go forward to data synthesis.

### Exclusion of minority measures

We considered what impact the exclusion of the minority measures had on the findings. To examine the contribution that each language assessment tool made to the transformed language measures, we plotted the distribution of transformed language measures over time, stratified by the original assessment tool and presented by language domain.

### Random or fixed effects

We examined the impact of including the data set identifier as the random effect or as a fixed effect using the Wu–Hausman test.<sup>108</sup> For simplicity, the comparison was based on a simple model of language change by baseline. The model was run twice, once with data set as a fixed effect and once with data set as a random effect. The differences between the estimates of the covariate and the standard error of the baseline score were used to calculate both the Wu–Hausman and the alternative Wu–Hausman for one parameter. If the  $W$ -score was  $< 3.841$  ( $\approx \chi^2$  with 1 degree of freedom), or the alternative  $W$  was  $< -1.96$  or  $> 1.96$  [ $\approx N(0,1)$ ], then we rejected the null hypothesis that random effects were more efficient.

### ***The inclusion of historic data sets***

We explored what bias there may have been in the inclusion of historic data sets (e.g. collected prior to the establishment of specialist inpatient stroke units), when approaches to the provision of stroke care differed.<sup>109,110</sup> Response to treatment may be influenced by overall health and improvements in stroke care, such as thrombolysis, which has been linked to better aphasia recovery.<sup>29</sup> Similarly, a response to SLT for aphasia depends on the therapy provided, and such approaches can change over time (as suggested by Godecke *et al.*<sup>56,72</sup>). We conducted a sensitivity analysis (RCT data sets only) to consider whether or not the recruitment date had any impact on recovery patterns by language domain.

### ***Excluding non-randomised controlled trial data sets***

We explored the impact of excluding data sets graded as being at a high risk of bias, in particular the non-RCT data sets, from the analysis. In each analysis (except the planned subgroup analysis; see *Subgroup analysis*), we analysed and presented the IPD gathered in the context of RCT studies before then conducting the analysis on the wider data set inclusive of non-RCT designs.

### ***Registry data sets and impact on findings***

We explored the impact and contribution that registry data sets (clinical and other research archives contributed to the RELEASE study) made to the analysis and considered whether or not these data sets may have altered the findings.

## **Subgroup analysis**

As time since stroke, age and stroke severity are likely to affect language recovery, we conducted subgroup analyses of these variables, in addition to including them as covariates in the modelling process.

## **Confidence in cumulative evidence**

We reviewed the quality of the data contributing to our analyses together with the quality of our meta-synthesis and analysis approaches and considered the impact this may have had on our confidence in the cumulative results. When appropriate, one researcher independently applied the GRADE approach<sup>111</sup> or similar tools to suggest a level of evidence.

## **Summary**

We established an international database of IPD gathered from pre-existing primary research and clinical data sets identified through a systematic review process. Contributions were invited and additional data sets were identified in the public domain. Language measures were transformed to a single anchor measure for each language domain. We explored patterns of language recovery over time among people with no access to SLT, access to historical SLT or SLT in the context of the primary research and participants' language performance at study enrolment. We explored the data for predictors of language recovery after aphasia. We undertook a one-stage IPD meta-analysis, incorporating network meta-analysis, to explore the impact of complex SLT interventions on language recovery for people with aphasia after stroke. We also considered whether or not specific therapy approaches were associated with the best language recovery outcomes for specific subgroups of people with aphasia.

# Chapter 3 Description of individual participant data, data sets and risk of bias

## Overview

In this chapter, we report the systematic review-informed development of the RELEASE database, the data sources and the data sets identified that were unavailable to us. We consider the design of the contributed data sets, the participant demographics, the language measures used, the risk of bias in the primary data sets, the data transformation and synthesis approaches, and risk of meta-biases.

## Results of the systematic search

Our search strategy identified 11,314 records; once duplicates were removed, we screened 5256 records for eligibility and excluded 2935 (*Figure 3*). After reviewing 2341 abstracts, 1210 were excluded and 1131 full texts were retrieved. The primary research teams that were linked to 698 references identified (including trial registrations), which appeared eligible for inclusion, were invited to confirm the eligibility and availability of the data set described in the identified report. We received 125 expressions of interest (see *Figure 3*).

We created a RELEASE study database of 174 data sets comprising 5928 IPD. Electronic data set contributions included 3940 out of 5928 IPD (66.5%) gathered in 75 out of 174 data sets (43.1%). A total of 1988 out of 5928 IPD (33.5%) appeared in 99 out of 174 (56.9%) eligible data sets reported in the public domain, and these were also included in our database (see *Figure 3*). Ineligible IPD (e.g. people with aphasia following traumatic brain injury) from mixed study population groups were excluded.

### Excluded data sets

We excluded 433, out of 1131, full texts that failed to meet our eligibility criteria; 77 data sets had fewer than 10 IPD; four data sets had qualitative data only; 272 data sets were not about aphasia, stroke or language impairment; and 52 were reviews, secondary data analysis or commentary pieces (see *Figure 3*).

### Unavailable data sets

We were unable to confirm whether or not the 267 remaining data sets identified as potentially eligible (reported across 399 records) met the RELEASE study inclusion criteria. Following careful review, it is possible that 53 were RCTs and 214 were a non-RCT design (see *Figure 3*). Of the 53 RCTs, 46 included, but did not necessarily evaluate, a SLT intervention.

## Included data sets

### Source

The date of participant recruitment was available for 79 out of 174 (45.4%) primary research studies (*Table 2*). These data sets reflected participants recruited from 1973 to 2016, although most were recruited since 2000 [67/79 (84.8%)]. Recruitment dates were unavailable for 95 out of 174 data sets (54.6%), particularly those from the public domain. We considered date of publication as a surrogate indicator of data set age [161/174 data sets (92.5%); 4627/5928 IPD (78%)]. Thirteen data sets did not have an associated publication, including recently completed research or clinical registries. Of the 161 data sets that were published between 1973 and 2017, most [135/161 (77.6%)] were published since 2000.

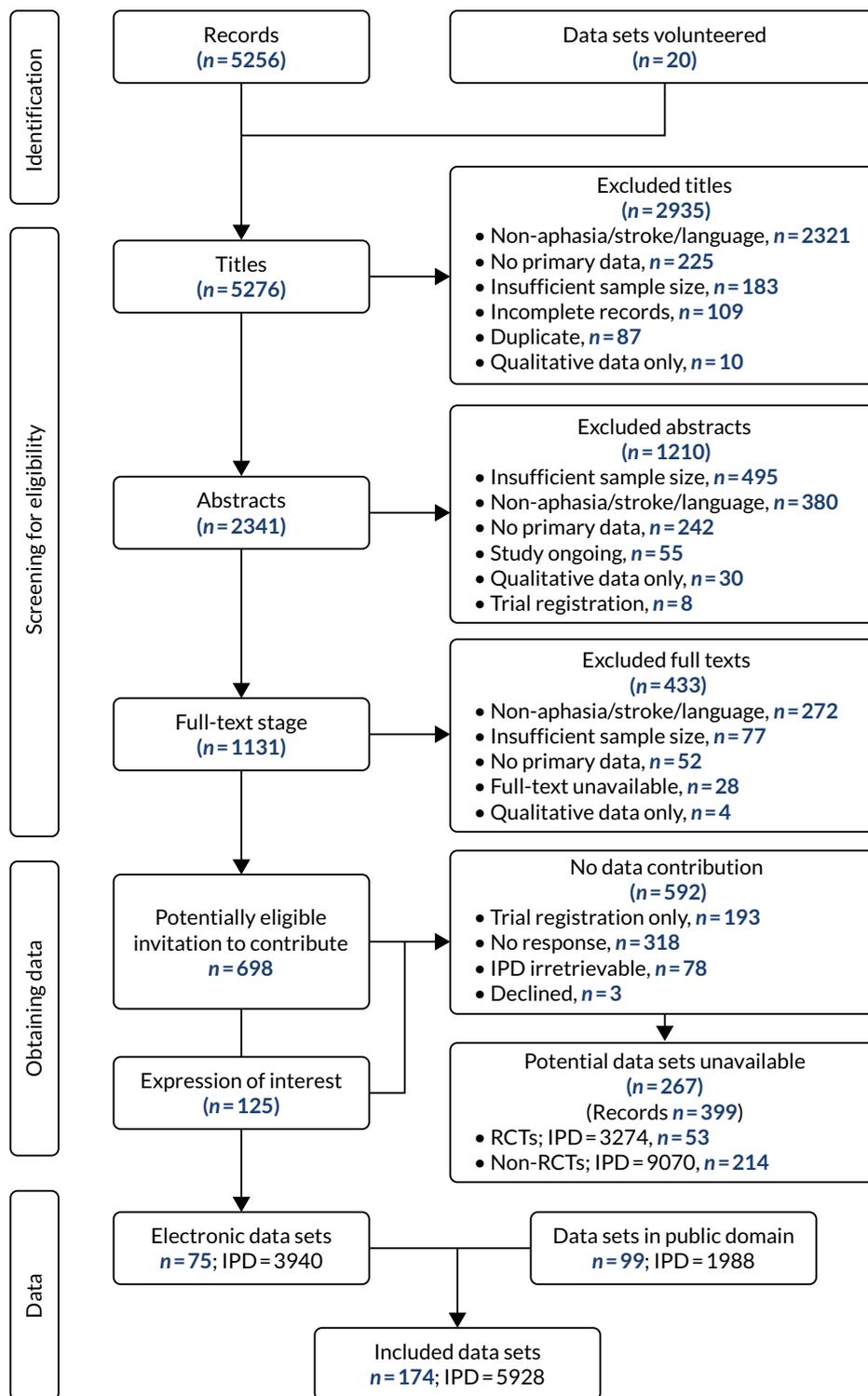


FIGURE 3 The PRISMA flow diagram indicating the search, identification, screening, exclusions, invitations to contribute and final data set. Reproduced with permission from Williams *et al.*<sup>112</sup> This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The figure includes minor additions and formatting changes to the original figure.

TABLE 2 Overview of studies in the RELEASE study database

Date of recruitment/publication or country	Data sets, n (%) (N = 174)	IPD, n (%) (N = 5928)
<b>Year of recruitment</b>		
1973	1 (0.6)	18 (0.3)
1974	1 (0.6)	24 (0.4)
1976	2 (1.1)	43 (0.7)
1981	1 (0.6)	155 (2.6)
1990	1 (0.6)	26 (0.4)
1993	1 (0.6)	119 (2.0)
1994	1 (0.6)	51 (0.9)
1995	1 (0.6)	50 (0.8)
1996	1 (0.6)	89 (1.5)
1998	1 (0.6)	57 (1.0)
1999	1 (0.6)	59 (1.0)
2000	2 (1.1)	101 (1.7)
2001	5 (2.9)	69 (1.2)
2002	1 (0.6)	36 (0.6)
2003	5 (2.9)	276 (4.7)
2004	4 (2.3)	122 (2.1)
2005	2 (1.1)	34 (0.6)
2006	7 (4.0)	568 (9.6)
2007	3 (1.7)	180 (3.0)
2008	6 (3.4)	198 (3.3)
2009	7 (4.0)	156 (2.6)
2010	6 (3.4)	239 (4.0)
2011	1 (0.6)	11 (0.2)
2012	7 (4.0)	426 (7.2)
2013	3 (1.7)	110 (1.9)
2014	1 (0.6)	39 (0.7)
2015	3 (1.7)	440 (7.4)
2016	4 (2.3)	477 (8.0)
Unreported	95 (54.6)	1755 (29.6)
<b>Publication date</b>		
1973-9	3 (1.7)	61 (1.0)
1980-9	8 (4.6)	287 (4.8)
1990-9	15 (8.6)	316 (5.3)
2000-4	19 (10.9)	562 (9.5)
2005-9	32 (18.4)	648 (10.9)
2010-14	68 (39.1)	2022 (34.1)
2015-17	16 (9.2)	731 (12.3)
Unpublished	13 (7.5)	1301 (22.0)

continued

TABLE 2 Overview of studies in the RELEASE study database (continued)

Date of recruitment/publication or country	Data sets, n (%) (N = 174)	IPD, n (%) (N = 5928)
<b>Country of study</b>		
Australia	14 (8.0)	295 (5)
Brazil	1 (0.6)	50 (0.8)
Canada	3 (1.7)	62 (1.0)
China	1 (0.5)	105 (1.8)
Croatia	1 (0.5)	13 (0.2)
Denmark	1 (0.5)	68 (1.2)
Egypt	1 (0.5)	29 (0.5)
Finland	1 (0.5)	36 (0.6)
France	2 (1.2)	121 (2.0)
Germany	17 (9.8)	420 (7.1)
Greece	1 (0.5)	38 (0.6)
Islamic Republic of Iran	2 (1.2)	77 (1.3)
Italy	11 (6.3)	230 (3.9)
Japan	3 (1.8)	75 (1.3)
The Netherlands	5 (2.9)	276 (4.7)
Belgium (and the Netherlands)	1 (0.5)	80 (1.4)
New Zealand	1 (0.5)	14 (0.2)
Norway	3 (1.8)	69 (1.2)
Poland	3 (1.8)	88 (1.5)
Portugal	3 (1.8)	74 (1.3)
Russian Federation	1 (0.5)	26 (0.4)
Republic of Korea	3 (1.8)	128 (2.2)
Spain	3 (1.8)	296 (5.0)
Sweden	3 (1.8)	333 (5.6)
Switzerland	2 (1.2)	26 (0.4)
Turkey	1 (0.5)	53 (0.9)
UK	30 (17.2)	1529 (25.8)
USA	56 (32.2)	1317 (22.2)
Total	174 (100.0)	5928 (100.0)

### Data set design

One-quarter of the primary research data sets included were RCTs [47/174 data sets (27.0%); 1778/5928 IPD (30.0%)]. The remainder were case series or cohort studies [104/174 data sets (59.8%); 2886/5928 IPD (48.7%)] and non-RCTs [18/174 data sets (10.3%); 411/5928 IPD (6.9%)]. Five data sets were derived from registries [5/174 data sets (2.9%); 853/5928 IPD (1.4%)]. Approximately half the data sets included a SLT intervention [91/174 data sets (52.3%); 2834/5928 IPD (47.8%)], whereas the remainder were non-interventional in nature.

In 20 data sets (11.5%; 311 IPD), participants crossed over from one intervention to another. An additional five data sets (2.9%; 240 IPD) delayed the start of treatment for a group. Seven data sets (4%; 128 IPD) allocated participants across three arms, and three data sets (1.7%; 84 IPD) allocated across four arms.

Some participants contributed to more than one data set, in some instances, participating in a follow-on study conducted by the same research group. In such cases, their demographic details were counted only once in our data set (e.g. *Table 3*). For other participants their language performance data had been duplicated across data sets. We identified these duplications and removed them from our database.

TABLE 3 Baseline characteristics of IPD<sup>a</sup> in the RELEASE study database

Participants (% of total IPD); data sets	IPD, n (%) (of reported) or median (IQR)
Sex: n = 5550 (93.6%); 158 data sets	
Female	2143 (38.6)
Male	3407 (61.4)
Age (years): n = 5785 (97.6%); 169 data sets	
Median (IQR)	63 (53–72)
Education (years): n = 3125 (52.7%); 84 data sets	
Median (IQR)	12 (10–16)
Handedness: n = 3879 (65.4%); 111 data sets	
Right	3719 (95.9)
Left	133 (3.4)
Ambidextrous	27 (0.7)
Ethnicity: n = 1475 (24.9%); 24 data sets	
White	1116 (75.7)
Asian	248 (16.8)
Black	67 (4.5)
Latino/Hispanic	9 (0.6)
Mixed	2 (0.1)
Other	33 (2.2)
Living context: n = 701 (11.8%); 21 data sets	
Living with others	473 (67.5)
Alone	146 (20.8)
Formal care environment	70 (10)
Mixed	12 (1.7)
Stroke type: n = 3416 (57.6%); 97 data sets	
Ischaemic	2795 (81.8)
Intracerebral haemorrhage	548 (16.0)
Subarachnoid haemorrhage	31 (0.9)
Mixed	42 (1.2)
Hemisphere: n = 4130 (69.7%); 130 data sets	
Left	3965 (96.0)
Right	81 (2.0)
Bilateral	84 (2.0)

continued

TABLE 3 Baseline characteristics of IPD<sup>a</sup> in the RELEASE study database (continued)

Participants (% of total IPD); data sets	IPD, n (%) (of reported) or median (IQR)
Time since stroke (days): n = 5841 (98.5%); 173 data sets	
Median (IQR)	321 (30–1156)
Prior stroke: n = 1274 (21.5%); 45 data sets	
Yes	110 (8.6)
No	1164 (91.4)
NIHSS: n = 716 (12.1%); 8 data sets	
Median (IQR)	11 (5–17)
mRS: n = 489 (8.2%); 6 data sets	
Median (IQR)	4 (3–4)
Barthel Index: n = 442 (7.5%); 5 data sets	
0–20 scale, median (IQR)	16 (9–20)
0–100 scale, median (IQR)	60 (15–95)
<b>Inclusion and exclusion criteria</b>	
Depression: n = 2075 (35.6%); 62 data sets	
Excluded/no depression	1723 (83.0)
Depression reported	352 (17.0)
Cognitive impairment: n = 3945 (66.5%); 100 data sets	
Excluded/no cognitive impairment	3347 (84.8)
Impairment reported	7 (0.2)
Cognitive score reported	591 (15.0)
Hearing impairment: n = 2848 (48.0%); 82 data sets	
Excluded/no hearing impairment	1767 (62.0)
Eligible for inclusion (including corrected hearing)	1081 (38.0)
mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.	
a Data are reflective of unique participants; when participants were enrolled in more than one study, the demographic descriptions have been amended as appropriate.	
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### People with aphasia

Of the 5928 people with aphasia following stroke represented in the RELEASE study database, 61.4% were male (3407/5928 IPD) and 38.6% (2143/5928) were female. They had a median age of 63 years (IQR 53–72 years). Most were right-handed [3719/3879 IPD (95.9%)]; the remainder were left-handed [133/3879 (3.4%)] or ambidextrous [27/3879 (0.7%)]. The median number of years of formal education, for those participants who had such information recorded [84/174 data sets (48.3%); 3125/5928 IPD (52.7%)], was 12 (IQR 10–16 years). Ethnicity was recorded for one-quarter of participants [1475/5928 IPD (24.9%)] across 24 out of 174 data sets (13.8%). Three-quarters of participants were from a White ethnic background [1116/1475 IPD (75.7%)]; the remainder were recorded as being of Asian [248/1475 (16.8%)], Black [67/1475 (4.5%)], Latino/Hispanic [9/1475 (0.6%)], Mixed [2/1475 (0.1%)] or Other [33/1475 (2.2%)] ethnic backgrounds (see Table 3).

## Living context

At the time of data collection, two-thirds of participants were living at home with other people [473/701 IPD (67.5%)], and one-fifth lived alone [146/701 (20.8%)], with a smaller number [70/701 (10.0%)] living in a formal care environment. This is based on information from 21 out of 174 data sets (12.1%) and 701 out of 5928 IPD (11.8%) (see *Table 3*).

## Language

The database was predominantly based on English-speaking participants [3162/5928 IPD (53.3%)]: the largest data set contributions were from the USA [56/174 data sets (32.2%); 1317/5928 IPD (22.2%)] and the UK [30/174 data sets (17.2%); 1529/5928 IPD (25.8%)]. The remaining data sets were collected across 22 other languages. One data set included bilingual data from 12 out of 5928 IPD (0.2%) (*Table 4*).

**TABLE 4** Languages of data collection based on 174 data sets and available IPD

Language	IPD, n (%)
Arabic	59 (1.0)
Cantonese	105 (1.8)
Croatian	13 (0.2)
Danish	68 (1.2)
Dutch	357 (6.0)
English	3162 (53.3)
Finnish	36 (0.6)
French	163 (2.8)
German	420 (7.1)
Greek	38 (0.6)
Greek/English	12 (0.2)
Italian	231 (3.9)
Japanese	75 (1.3)
Korean	128 (2.2)
Mandarin	23 (0.4)
Norwegian	69 (1.2)
Patois	1 (0.02)
Persian	47 (0.8)
Polish	88 (1.5)
Portuguese	124 (2.1)
Russian	26 (0.4)
Spanish	297 (5.0)
Swedish	333 (5.6)
Turkish	53 (0.9)
Total	5928 (100.00)

## Stroke

Among those for whom we had information on time since stroke [5841/5928 IPD (98.5%)] the median time since stroke was 321 (IQR 30–1156) days. When reported, this was mostly in the left hemisphere [3965/4130 (96.0%)], ischaemic [2795/3416 (81.8%)] and, in most cases, their first stroke [1164/1275 (91.4%)] (see *Table 3*).

Stroke severity at study entry was moderate to severe on the National Institutes of Health Stroke Scale (NIHSS) [median score 11 (IQR 5–17); 8/174 data sets (4.6%); 716/5928 IPD (12.1%)], the modified Rankin Scale (mRS) [median score 4 [IQR 3–4]; 6/174 data sets (3.4%); 489/5928 IPD (8.2%)] and the Barthel Index [the 0–100 scale: median score 60 (IQR 15–95); the 0–20 scale: median score 16 (IQR 9–20); 5/174 data sets (2.9%); 442/5928 IPD (7.5%)]. Interestingly, despite all included participants having aphasia, all stroke and disability scales included participants who had no stroke symptoms [NIHSS = 0; 15/716 IPD (2.1%)], no symptoms at all [mRS = 0; 6/489 IPD (1.2%)] or scored as ‘independent’ [Barthel Index = 100; 48/442 IPD (10.9%)] (see *Table 3*).

## Concomitant symptoms

Cognitive impairment was an inclusion or exclusion criteria for 100 out of 174 data sets (57.5%) involving 3945 out of 5928 IPD (66.5%), of whom 7 IPD participants were recorded as having a cognitive impairment. Cognitive scores were available for 591 out of 3945 IPD (15.0%), and an additional 3347 IPD (84.8%) participants did not have a cognitive impairment. Similarly, depression was listed in the inclusion or exclusion criteria for 62 out of 174 (35.6%) data sets relating to 2075 out of 5928 IPD (35.0%). Depression was reported for 352 out of 2075 IPD (17.0%) participants; most [1723/2075 IPD (83.0%)] were not depressed.

## Measures of language

All data sets included IPD on one or more of the following language outcomes: overall language ability [2699/5928 IPD (45.5%); 80/174 data sets (46.0%)], auditory comprehension [(2750/5928 IPD (46.4%); 71/174 data sets (40.8%)], naming [2886/5928 IPD (48.7%); 75/174 data sets (43%)], other spoken language [380/5928 IPD (6.4%); 9/174 data sets (5.2%)], reading comprehension [770/5928 IPD (13.0%); 12/174 data sets (6.9%)], writing [724/5928 IPD (12.2%); 13/174 data sets (7.5%)], functional communication observer-rated [1591/5928 IPD (26.8%); 29/174 data sets (16.7%)], functional communication self-rated [68/5928 IPD (1.1%); 3/174 data sets (1.7%)] and discourse analysis [213/5928 IPD (3.9%); 5/174 data sets (2.9%)] (*Table 5*).

## Speech and language therapy interventions

We identified 91 out of 174 data sets (52.3%) [2746/5928 IPD (46.3%)] that delivered a SLT intervention. Two registry data sets included some participants in receipt of SLT, but the interventions were not standard across the data set and were inconsistently recorded, so these were excluded from our analysis of the impact of SLT components on outcomes. Language outcome data availability at baseline and at the end of intervention limited the number of data sets that could inform our planned intervention analysis to 67 out of 174 (38.5%) data sets [2330/5928 IPD (39.3%)] (*Table 6*).

Interventions included conventional therapy [8/67 data sets (11.9%); 529/2330 IPD (22.7%)], social support [2/67 data sets (3.0%); 169/2330 IPD (7.3%)] or a defined SLT intervention that could be categorised by impairment target or theoretical approach [62/67 data sets (92.5%); 1456/2330 IPD (62.5%)] (see *Table 6*). Twenty of these defined SLT interventions included a pharmacological or electrical brain stimulation co-intervention, which may have contributed to language outcomes [20/67 data sets (29.8%); 423/2330 IPD (18.1%)]. Eleven data sets included a comparison group that had no access to therapy [11/67 data sets (16.4%); 167/2330 IPD (7.2%)]. One intervention targeted change in

TABLE 5 Data availability

IPD	Language outcome, n (N data points) [n data sets]								
	Overall language ability	Auditory comprehension	Naming	Other spoken language	Reading comprehension	Writing	Functional communication (observer rated)	Functional communication (self-rated)	Discourse analysis
Collected data	2699 (5123) [80]	2750 (5834) [71]	2886 (5130) [75]	380 (621) [9]	770 (1085) [12]	724 (1061) [13]	1591 (5085) [29]	68 (268) [3]	213 (423) [5]
Merged with demographic data	2684 (5108) [80]	2728 (5783) [71]	2810 (4928) [73]	380 (621) [9]	729 (980) [11]	684 (957) [12]	1563 (5021) [29]	68 (268) [3]	213 (423) [5]
Merged with intervention data	929 (2338) [29]	1058 (2969) [31]	1149 (2701) [37]	250 (491) [7]	200 (309) [6]	136 (249) [8]	989 (3394) [21]	43 (218) [2]	97 (258) [2]
Removed duplicate records	929 (1939) [29]	1055 (2021) [31]	1018 (2189) [37]	250 (491) [7]	200 (309) [6]	136 (249) [8]	984 (2084) [21]	43 (123) [2]	97 (258) [2]
Exclude trials with no baseline or no follow-up data	704 (1714) [18]	695 (1732) [21]	672 (1843) [22]	238 (479) [6]	160 (269) [4]	98 (211) [6]	818 (1918) [19]	43 (123) [2]	97 (258) [2]
Exclude non-RCT IPD	524 (1351) [11]	591 (1485) [16]	419 (1302) [13]	187 (369) [3]	11 (33) [1]	47 (104) [3]	697 (1632) [14]	11 (28) [1]	97 (258) [2]
Exclude IPD with no baseline or no follow-up data	488 (488) [11]	556 (556) [16]	391 (391) [13]	182 (182) [3]	11 (11) [1]	47 (47) [3]	544 (544) [14]	11 (11) [1]	90 (90) [2]

TABLE 6 Interventions in the RELEASE study database

Participants	IPD, n (%) (N = 2330)	Data sets (N = 67)
<b>Overall intervention group</b>		
No therapy	167 (7.2)	11
Social support	169 (7.3)	2
SLT (defined)	1456 (62.5)	62
Conventional	529 (22.7)	8
<b>SLT intervention delivery</b>		
Days since stroke onset	2084 (89.4)	64
<b>Mode of delivery</b>		
Face to face	1957 (84.0)	60
Computer	315 (13.5)	15
Telephone	15 (0.6)	1
Self-management	106 (4.5)	4
<b>Living context</b>		
Alone	88 (3.8)	7
Formal care environment	39 (1.7)	3
With others	195 (8.4)	9
<b>Therapy setting</b>		
Health-care setting (clinic, hospital, rehabilitation centre, therapy clinic, university)	1866 (80.1)	48
Home (home, community)	575 (24.7)	17
<b>Therapy theoretical approach</b>		
Functional/pragmatic	246 (10.6)	8
Phonological	124 (5.3)	9
Semantic and phonological	260 (11.2)	15
Semantic	34 (1.5)	2
Constraint-induced aphasia therapy	113 (4.8)	7
Melodic intonation therapy	61 (2.6)	4
<b>Therapy language rehabilitation target</b>		
Mixed auditory comprehension and spoken language	583 (25.0)	20
Auditory comprehension	68 (2.9)	4
Reading	10 (0.4)	1
General spoken-language expression	245 (10.5)	11
Word-finding	489 (21.0)	30
Co-intervention	423 (18.2)	15
<b>Therapy context</b>		
One to one	1613 (69.2)	47
Self-management	84 (3.6)	6
Group	148 (6.4)	8
Mixed	207 (8.9)	9

TABLE 6 Interventions in the RELEASE study database (continued)

Participants	IPD, n (%) (N = 2330)	Data sets (N = 67)
<b>Provider</b>		
Professional	1871 (80.3)	62
Non-professional	274 (11.8)	7
Self-management	10 (0.4)	1
Intensity (hours per week)	1882 (80.8)	60
Frequency (number of sessions per week)	2057 (88.3)	66
Duration (total number of days, start to finish)	1960 (84.1)	64
Dose (hours of SLT)	1978 (84.9)	62
Home practice (yes/no)	1306 (56.1)	31

communication behaviours among a health-care professional group and so did not contribute to our analysis of SLT interventions delivered to people with aphasia.

### Intervention context

Most participants receiving an intervention lived at home with others [195/2330 IPD (8.4%)]. Interventions were typically delivered in a formal health-care setting [1866/2330 IPD (80.1%)] on a one-to-one [1613/2330 IPD (69.2%)], face-to-face [1957/2330 IPD (84.0%)] basis, where therapy was provided by a professional [1871/2330 IPD (80.3%)] (see Table 6).

### Intervention description

Therapy targeted a range of language impairments including spoken language and/or naming [734/2330 IPD (31.5%)], auditory comprehension [68/2330 IPD (2.9%)], mixed spoken language and auditory comprehension [583/2330 IPD (25%)] and reading [10/2330 IPD (0.4%)]. No intervention specifically targeted the rehabilitation of writing. Most of the spoken-language interventions targeted improvements on naming (also known as word-finding) therapy [489/2330 IPD (21%)].

A range of theoretical approaches were identified, including semantic [34/2330 IPD (1.5%)], phonological [124/2330 IPD (5.3%)], semantic and phonological [260/2330 IPD (11.2%)], constraint-induced aphasia therapy [113/2330 IPD (4.8%)], melodic intonation therapy [61/2330 IPD (2.6%)] and functional-pragmatic therapy approaches [246/2330 IPD (10.6%)].

### Intervention regime

We gathered data on the frequency [2057/2330 IPD (88.3%); 66/67 data sets (98.5%)], duration [1960/2330 IPD (84.1%); 64/67 data sets (95.5%)], intensity [1882/2330 IPD (80.8%); 60/67 data sets (89.6%)] and dosage [1978/2330 IPD (84.9%); 62/67 data sets (92.5%)] of the SLT interventions. Information on whether or not the SLT intervention had been tailored by difficulty of the tasks was available for 1145 out of 1373 IPD (83.4%) [34/67 data sets (50.7%)]; information on whether or not the SLT intervention had been tailored by functional relevance to the individual participant was available for 649 out of 928 (69.9%) IPD [22/67 data sets (32.8%)]. Whether or not participants had been prescribed home-based practice tasks was available for 1306 out of 2330 IPD (56.1%) [31/67 data sets (46.3%)] (see Table 6).

### Risk of bias

The sample size of the primary research data sets ranged from 10 IPD of people with aphasia after stroke [25/174 data sets (14.4%)] to one data set with 420 IPD. An overview of each contributing data set can be found in *Report Supplementary Material 1*, but a summary is provided in *Quality of primary research data sets*.

## Quality of primary research data sets

### Selection bias

A total of 47 RCTs were included in the RELEASE study. Of these, 27 employed an adequate approach to the generation of the random number sequence (such as a random numbers table). Concealment of allocation was confirmed in 22 RCTs. We also included 18 non-RCTs that did not employ randomisation.

When data availability permitted, we checked individual RCT comparison groups at baseline for similarity. We identified six out of 47 RCTs for which there was a significant between-group difference at baseline by reported age (3/45 RCTs), sex (1/45 RCTs), time since stroke (2/45 RCTs) and language impairment (1/45 RCTs) (see *Appendix 4, Table 12*). Only two out of nine non-RCT group comparison data sets were found to differ at baseline in relation to reported time since stroke (see *Appendix 5, Table 13*) and one dataset differed with regard to sex (see *Appendix 5, Table 13*).

### Detection bias

Although participant blinding in SLT studies is often unachievable, the blinding of outcome assessors is important when considering risk of bias and can usually be achieved. Blinding of outcome assessors was reported in 48 out of 174 data sets (27.5%), and an additional 9 out of 174 (5.2%) data sets described partial blinding (blinding for a subset of data) for participants. The remaining 117 data sets either did not report on blinding (92/117) or clearly indicated that blinding was not present (25/117). These figures reflect the use of blinding across all data sets in the RELEASE study database. In many cases, blinding was simply irrelevant to the primary purpose of that data set (e.g. a clinical registry or observational study). Risk of detection bias will be considered more specifically in relation to our analysis in *Chapters 6 and 8*.

### Attrition bias

One-third of data sets [58/174 (33.3%)] reported participants who failed to complete the study (i.e. who dropped out). Such withdrawals are to be expected in a participant population after stroke. However, although there is a risk of incomplete outcome data, most researchers provided details of dropouts (for any reason) and of those who did not adhere to the intervention. By contrast, 116 out of 174 data sets did not report any loss of participants over time.

### Reporting bias

We identified a risk of reporting bias among data sets that were only partially represented in the RELEASE study database. One-third of included IPD [1988/5928 IPD (33.5%); 99/174 data sets (56.6%)] were extracted from the public domain. Although some data sets were fully reported in the public domain, most were only partially available (e.g. baseline data only).

Similarly, some primary research data set electronic contributions were also incomplete. Cross-referencing with the published reports indicated that additional data items were available at the point of publication. It is possible that some data items (e.g. IPD on therapy dosage) had not been stored electronically as part of the main data set or had been lost over time.

### Other biases

Inclusion and exclusion criteria were available for 170 out of 174 (97.7%) and 120 out of 174 (69.0%) of the data sets, respectively. Both inclusion and exclusion criteria were reported by 115 out of 174 (66.1%) data sets. Eight data sets were based on retrospective data collection [8/174 (4.6%)]. Eleven out of 174 (6.3%) data sets were collected in the context of primary research studies that aimed to develop or validate an outcome measure or assessment. One intervention study targeted arm movement recovery, whereas the SLT intervention functioned as an attention control intervention (32 IPD).

Other quality data items included reporting on the context of data collection (2441 IPD) and the presence of co-interventions (423 IPD). We planned to consider these items in our analysis and interpretation of findings. Adherence to a SLT intervention was captured for only 27 out of 91 (29.7%) intervention data sets.

## Data synthesis

### Transformations

A total of 64 assessments were used across data sets to capture participants' language performance. Some assessments comprised several subtests, which also contributed to the data synthesis for other language domains [e.g. Western Aphasia Battery (WAB) data contributed to overall language ability, auditory comprehension, naming and reading outcomes]. Language-specific adaptations of an original assessment were profiled individually to accommodate differences between languages.

We collated and categorised each assessment and their relevant subtests by language domain. For each data set, we noted the scoring format. Data from some tools [e.g. the Token Test (TT)] were reported in raw scores, percentiles, *t*-scores and error scores and were either positively or negatively scored. All scores were converted to raw scores and positive scoring.

For each language domain, we identified the assessment used by the most data sets as the 'anchor measure' (see *Appendix 7, Table 14*). In most cases, this choice also reflected the assessment with the greatest availability of IPD. The availability of IPD on an assessment contributed to the choice of anchor measure only in situations in which the greatest number of data sets using an assessment was shared across an equal number of data sets.

We examined the contribution that each assessment made to the overall data for that language domain and plotted the distribution of each score at baseline across increasing time since stroke time points and stratified by the original assessment (see *Appendix 6, Figure 27*). We concluded that the data points generated by each of the minority and anchor measures were valid and within the expected ranges.

The maximum, minimum, median, lower quartile (LQs) and upper quartile (UQs) were calculated for each of the identified anchor measures (see *Appendix 7, Table 14*). The values for the maximum, minimum, median, LQ and UQ were calculated for each of the remaining assessment tools that captured that language domain (minority measures). These values were then transformed to the anchor measure scale, ensuring that the values remained within the minimum and maximum values of the anchor measure scale (see *Appendix 7, Table 14*).

For each analysis, we collated the data with other required data items (e.g. participant demographic data items or intervention data), which resulted in a reduction of overall data to inform our analysis. We profile this drop-off in data availability in *Table 5*.

## Risk of bias in our individual participant data meta-analyses

### Selection bias in data set recruitment

The systematic review-based approach to the identification of eligible data sets recruited an additional 122 data sets to those originally identified through our research network alone, yielding important demographic and language IPD. For example, our final database has 5928 IPD on time since stroke (our original recruitment estimate was 3181 IPD) and 2922 IPD on naming outcomes (originally estimated as 2007 IPD). Methodologically, employing a review-informed approach to building the

database was essential. It reduced the risk of bias from an analysis based only on data sets contributed through pre-existing networks and increased the feasibility of analysis on a sparse database with limited overlap in outcomes and demographic data across data sets.

### ***Publication bias in data set recruitment***

Overall, the database included data sets collected across 28 countries and 23 international languages (see *Tables 2 and 4*). We included 13 unpublished data sets. We considered the risk of publication bias by examining the proportion of significantly reported results by decade or other suitable period grouping. Any suggested imbalance was tested with the chi-squared test (and is reported in *Chapter 8*).

### ***Availability bias in data set recruitment***

In the systematic review, we identified 399 out of 698 (57.2%) records reporting 267 potentially eligible data sets, which, despite best efforts, were not included (see *Report Supplementary Material 2*). Of these, 53 data sets appeared to be RCTs, with 46 out of the 53 RCTs including a SLT intervention that was part of the study protocol or standard care. Of the 47 RCTs that contributed group summary level data to the Cochrane review meta-analysis of SLT for aphasia after stroke,<sup>41</sup> we secured IPD for 17. We also secured IPD from five RCTs that were 'ongoing' at the time of the Cochrane review<sup>41</sup> and from a further four RCTs that were identified but unavailable to the Cochrane review.<sup>41</sup>

## **Summary**

We created an international database of 5928 IPD on people with aphasia after stroke, gathered from 174 data sets from across 28 countries. Half of the data sets were based on an English-speaking population, one-quarter were RCTs and 13 were unpublished. All data sets included participants for whom data were available on time since the index stroke and a measure of language impairment on overall language ability, auditory comprehension, spoken language (including naming), reading comprehension, writing or functional communication. Within this, approximately half of the dataset had a language measurement as well as corresponding data on baseline demography. Half of the included data sets referred to a SLT intervention.

Interventions were wide-ranging and classification of SLT approach by impairment target and theoretical approach required a consensus approach. We considered risk of bias both at the primary data set level and at the meta-analysis level and, when possible, took methodological approaches to address any risk of bias or to consider its possible impact when interpreting the findings. We transformed all language measures to a single anchor measure for each language domain and filtered IPD based on the overlapping availability of the required variables for each planned analysis.

# Chapter 4 Language recovery after stroke

## Overview

We explored aphasia recovery after stroke using eligible data from across the database, as relevant for each analysis. We investigated:

1. the natural history of language recovery in participants with no access to SLT
2. language recovery over time in participants with access to SLT
3. distribution of language scores at study entry
4. change in scores from baseline to first follow-up after study access to SLT.

## Natural history of language recovery

To meet the criteria for the natural history population, participants had to be enrolled in the primary study within 15 days of their first stroke and allocated to a no-SLT group. For these participants, only one data set reported IPD on overall language ability ( $n = 61$ ), auditory comprehension ( $n = 6$ ), naming ( $n = 6$ ) or functional communication (observer-rated activity and participation, both  $n = 51$ ), respectively. As we had prespecified that we would not base an analysis on a single data set, there were insufficient data to ascertain the natural history of language recovery in relation to these domains for this population. For the remaining domains (other spoken language, reading comprehension and writing), we identified no eligible IPD for exploring natural history of language recovery.

## Language recovery over time in participants with study access to speech and language therapy

We examined the pattern of language recovery over time in each language domain for participants who had access to SLT during the primary study. We also examined language recovery among participants who were allocated to receive no SLT during the primary study. These participants were not considered in our natural history analysis as they were enrolled beyond 15 days of index stroke, and we had clear evidence or reasonable grounds to assume that they had historical access to SLT as part of standard health care before the start of the study. When participants were allocated to receive no therapy intervention in the primary study but were permitted access to SLT after the active comparison period had been completed, we truncated our analysis of follow-up to the first assessment following the study intervention period, thus excluding any impact of later access to SLT in this group.

### *Trajectory of overall language ability over time*

We examined the trajectory of overall language ability over time by looking at scores on aphasia test batteries transformed to the anchor measure [Western Aphasia Battery-Aphasia Quotient (WAB-AQ)], in which higher scores indicated better language performance. We had no data capturing overall language ability over time for participants who had received only historical SLT in the RCT population, meaning we could not conduct comparative analyses with the participants who had SLT during the primary studies on this population. We therefore present the trajectory of overall language ability scores over time for participants allocated to SLT in RCTs (601 IPD; 18 RCTs; *Figure 4a*) and across all study designs (2345 IPD; 74 data sets; see *Figure 4b*). In both cohorts, there was a trend towards increased scores on aphasia language batteries over time.

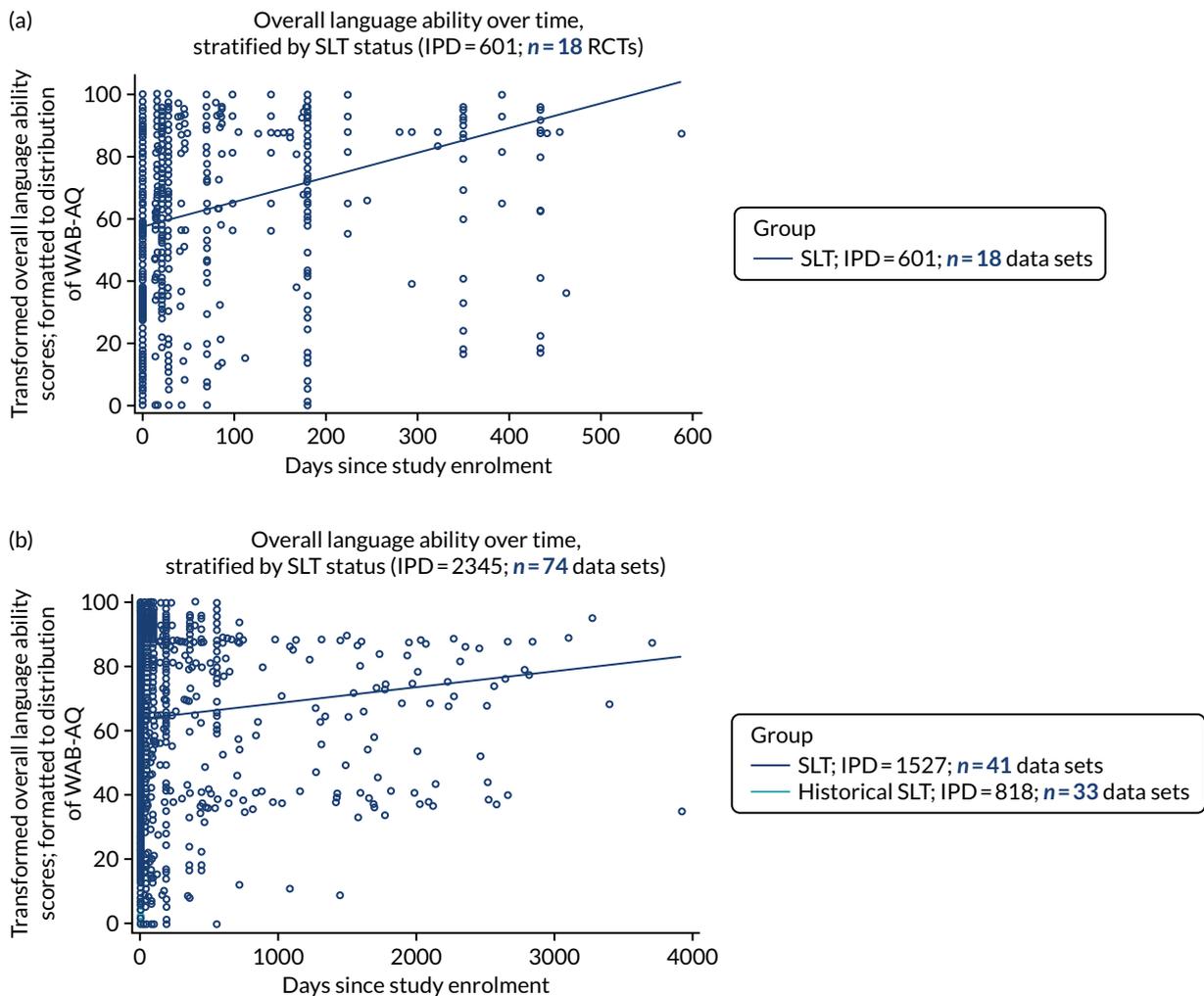


FIGURE 4 Overall language ability scores over time. (a) RCTs; and (b) all study types.

### Trajectory of auditory comprehension over time

In our database, all participants who were allocated to receive no study-based SLT went on to receive SLT after the study intervention period was over. Due to inadequate longer-term follow-up assessments beyond the study intervention period, we could not describe the trajectory of auditory comprehension scores over longer time periods in those allocated to SLT versus those who received only historical SLT. We examined the trajectory of auditory comprehension scores over time in both the RCT population (536 IPD; 17 data sets; *Figure 5a*) and using all study designs (2463 IPD; 62 data sets; see *Figure 5b*). The anchor measure was Token Test from the Aachen Aphasia Test (TT-AAT).

Of 536 IPD from 17 RCTs, 521 IPD (17/17 RCTs) were allocated to receive a SLT intervention, whereas 15 IPD (2/17 RCTs) received historical SLT only (see *Figure 5a*). Those with historical SLT experienced a decline in their auditory comprehension scores over time. In contrast, those who had study access to SLT experienced an increase in auditory comprehension scores over time. We examined this trajectory more closely by plotting follow-up between the two groups up to 90 days (see *Figure 5c*).

Despite randomisation, we observed slightly higher initial auditory comprehension scores at baseline in the historical SLT group; this declined over time. Across all primary research study designs (2463 IPD; 62 data sets; see *Figure 5b*), participants allocated to receive SLT demonstrated an increase in auditory comprehension scores over time. Data from participants who received only historical SLT in this population were available at only three time points and were therefore too sparse to make strong inferences (see *Figure 5d*).

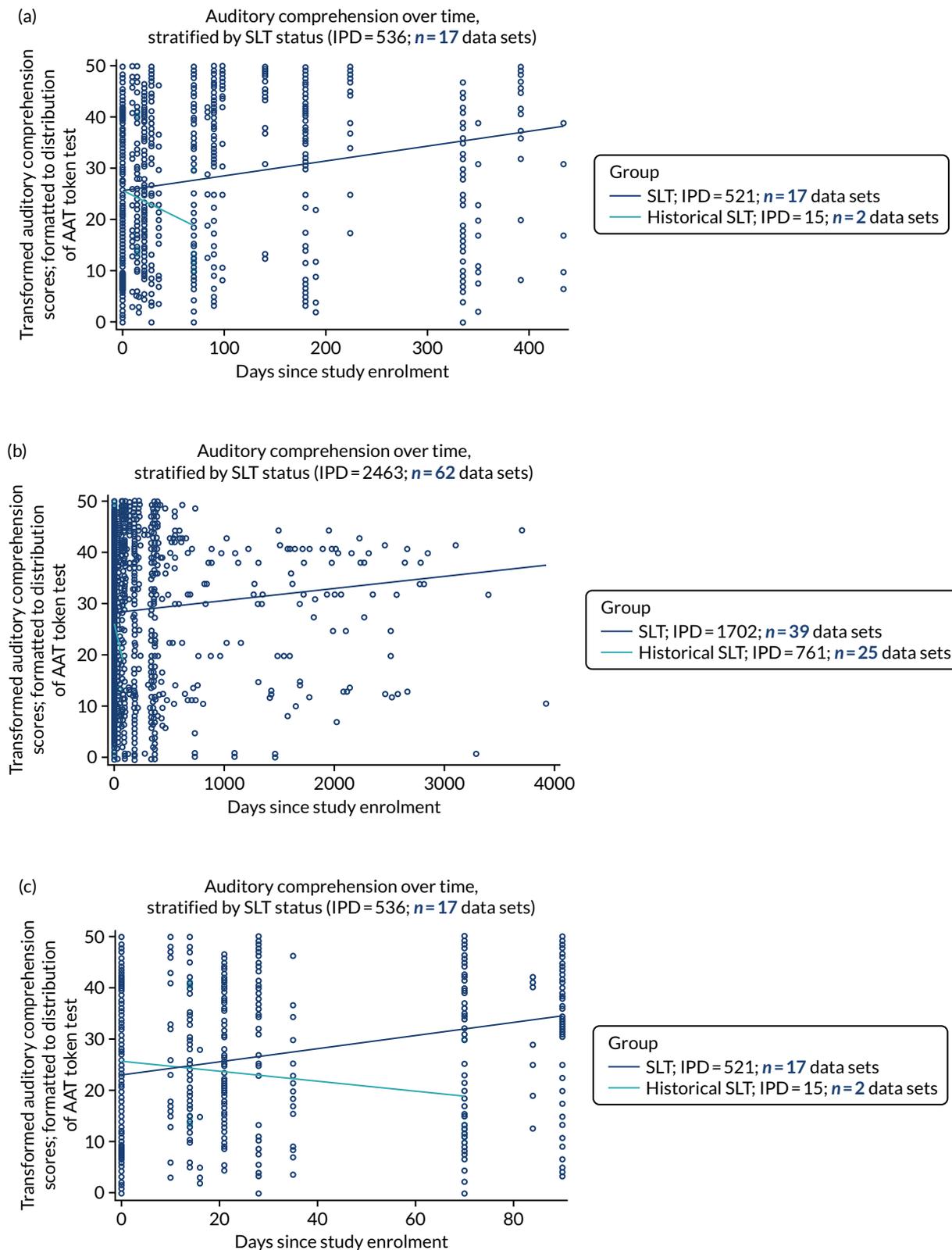


FIGURE 5 Auditory comprehension scores over time. (a) RCTs; (b) all study types; (c) within earlier follow-up times in RCTs; and (d) earlier follow-up times in all study types. (continued)

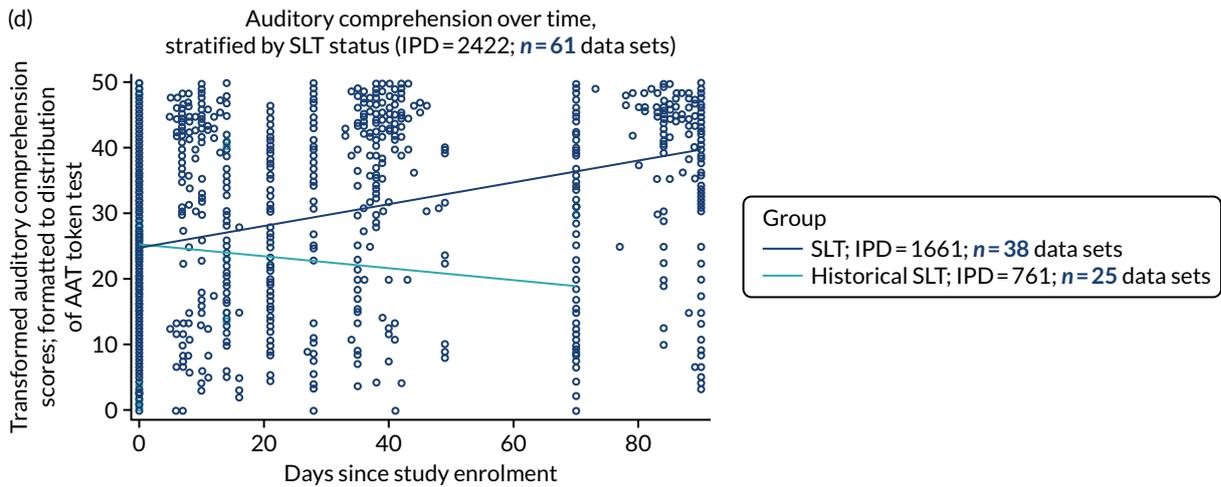


FIGURE 5 Auditory comprehension scores over time. (a) RCTs; (b) all study types; (c) within earlier follow-up times in RCTs; and (d) earlier follow-up times in all study types.

### Trajectory of naming over time

We transformed all naming scores to the Boston Naming Test (BNT) distribution. There were inadequate naming data at follow-up time points immediately after study intervention comparison periods from historical SLT participants in the primary studies (29 IPD; 3 RCTs). We therefore could not compare the trajectory of naming scores over longer follow-up time periods between participants with study access to SLT and participants with historical access to SLT in the RCT population. Instead, we present the trajectory of naming scores over shorter follow-up times (up to 90 days) for participants in RCTs (623 IPD; 22 RCTs; *Figure 6a*) and across all study designs (2592 IPD; 68 data sets; see *Figure 6b*).

Historical SLT participants had higher naming scores at baseline than those allocated to receive SLT. Naming scores appeared to decline over time for the historical SLT participants, whereas scores for the SLT group experienced a steady upwards trajectory over time (see *Figure 6a-c*). Across all study types, there were limited data on naming scores among the historical SLT participants. For those who had study SLT access, naming scores increased with time (2592 IPD; 68 data sets; see *Figure 6b*).



FIGURE 6 Naming scores over time. (a) RCTs; (b) all study types; and (c) within earlier follow-up times in RCTs. (continued)

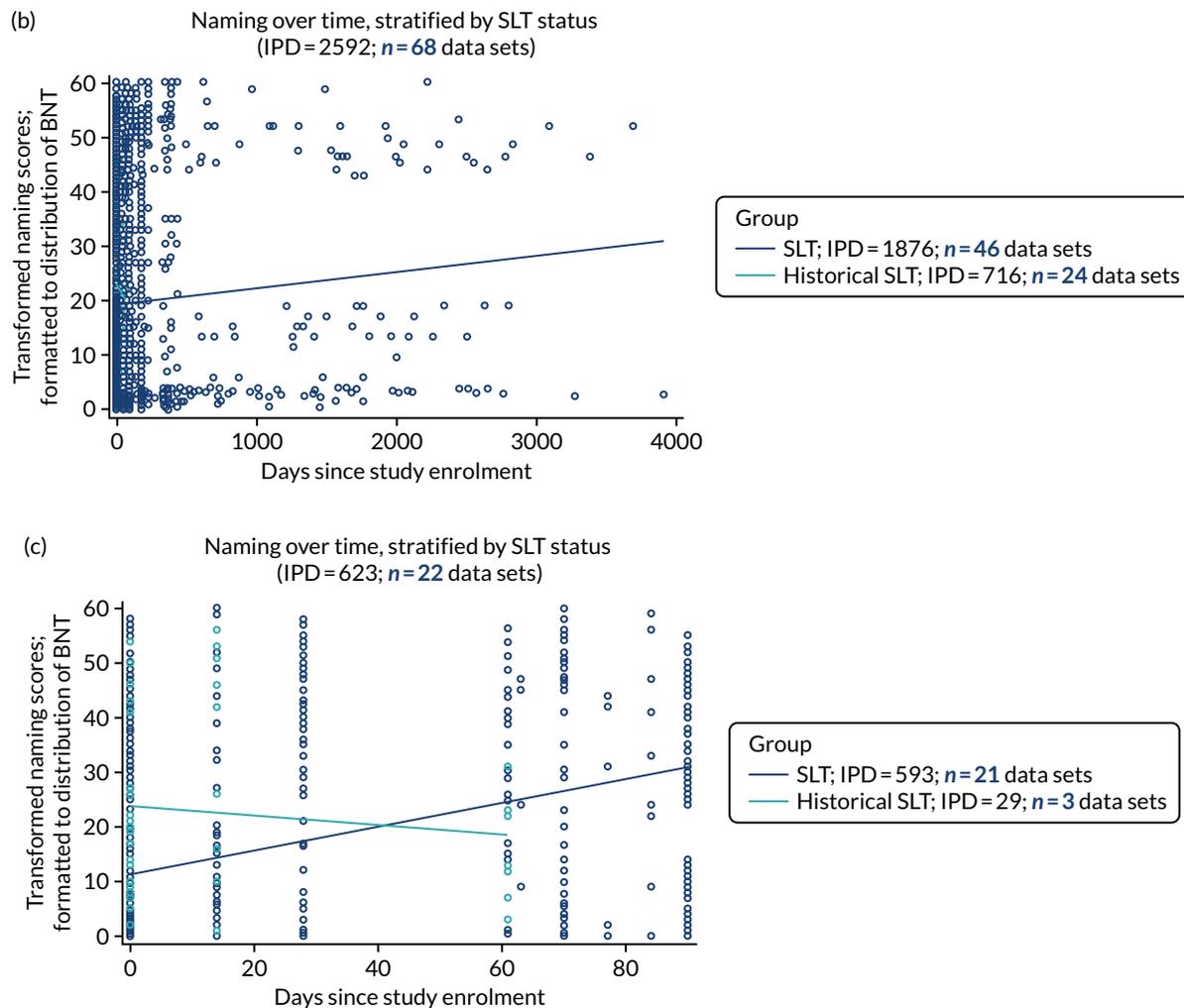


FIGURE 6 Naming scores over time. (a) RCTs; (b) all study types; and (c) within earlier follow-up times in RCTs.

### Trajectory of other spoken language over time

There were no data available on other spoken-language outcomes for participants who received only historical SLT in RCTs. This meant that we could not describe the trajectory of spoken-language scores among this group or make any comparison with the trajectory of spoken-language scores over time among participants allocated to study SLT. We therefore present the trajectory of spoken-language scores over time [transformed to the verbal (1) subtest of the Porch Index of Communicative Ability (PICA)] for participants allocated to SLT in a RCT (172 IPD; 3 RCTs; *Figure 7a*) and across all study types (353 IPD; 8 data sets; see *Figure 7b*). The trajectory appeared to be stable over time in both populations.

### Trajectory of reading comprehension over time

We reviewed the transformed reading comprehension scores [transformed to fit the range of the Comprehensive Aphasia Test (CAT) reading subtest] for historical SLT participants and for those who had access to SLT in the primary studies. All historical SLT participants were permitted access to conventional SLT beyond the active intervention comparison period. Reading comprehension data beyond the immediate study intervention periods were inadequate for comparative meta-analysis. The stable trajectory of available reading comprehension scores over time among participants who had SLT across all primary studies is presented in *Figure 8* (650 IPD; 9 data sets).

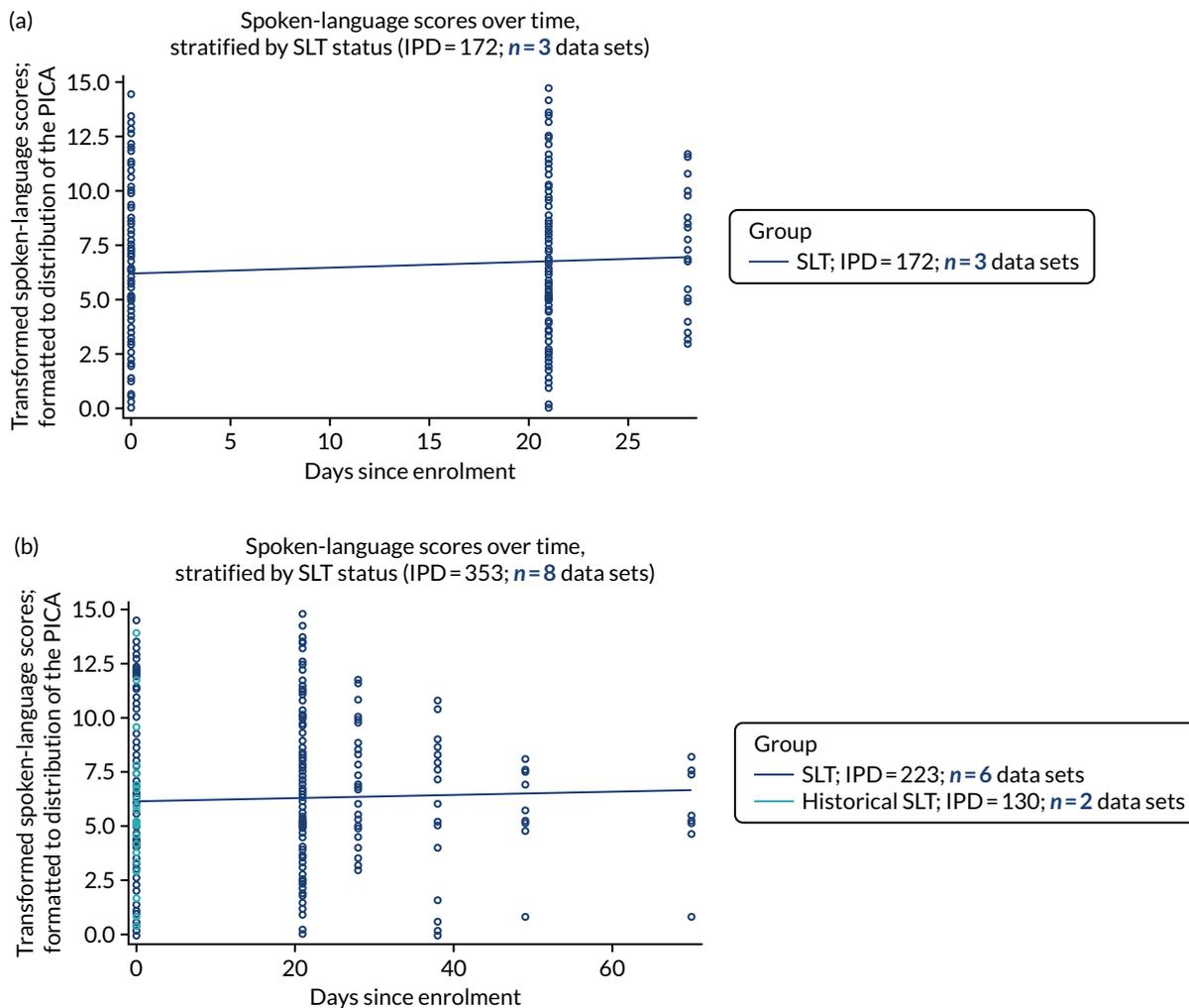


FIGURE 7 Other spoke language scores over time. (a) RCTs; and (b) all study types.

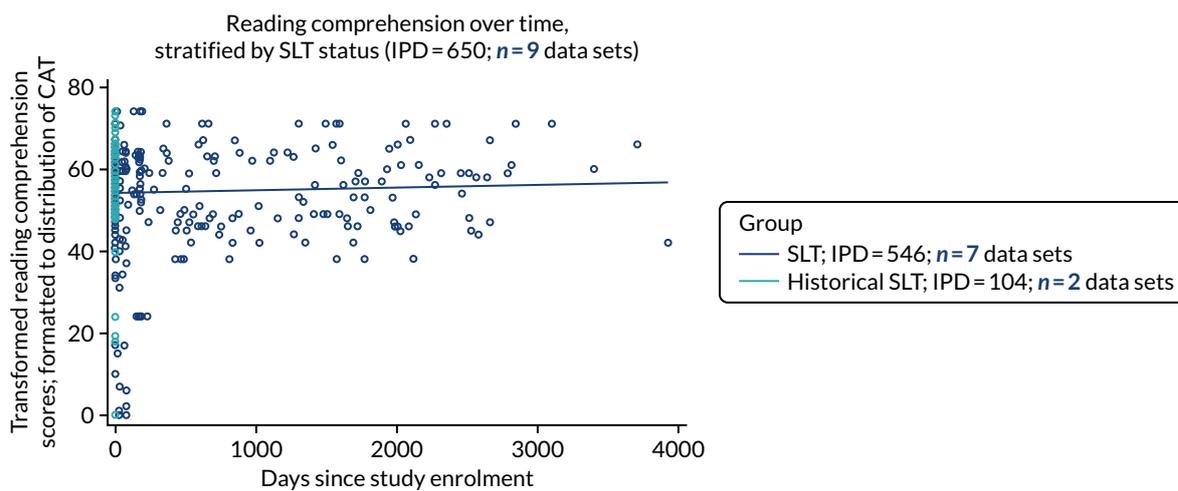


FIGURE 8 Reading comprehension scores over time for all study types.

### Trajectory of writing over time

Participants with available writing scores who received only historical SLT during the primary studies were typically given access to SLT immediately after the study intervention comparison period. Thus, writing data from later follow-up time points were insufficient to permit comparative meta-analysis by SLT status over time. We report writing data from SLT participants only. Data from three RCTs (41 IPD; *Figure 9a*) suggest a slight score decline across time. Across all study types (635 IPD; 10 data sets; see *Figure 9b*), following transformation to the anchor score (CAT writing subtest), we observed stable writing scores over time.

### Trajectory of observer-rated functional communication (activity) over time

For functional communication (activity) over time, we examined 828 IPD from 17 RCTs (*Figure 10a*). The anchor measure for functional communication domain (activity) was the Aachen Aphasia Test-Spontaneous Speech Communication (AAT-SSC). There were inadequate data on participants who received only historical SLT, which did not permit comparison of trajectories with the SLT group; once again, there were few after-intervention data points and people who received only historical SLT during the study were all permitted to receive SLT after the intervention period was complete. In the SLT group, we observed better observer-rated activity scores over time. This was also evident when looking at all study types (1272 IPD; 28 data sets; see *Figure 10b*). Data on observer-rated participation measures showed the same patterns for better participation scores over time (see *Report Supplementary Material 3, figure 1*).

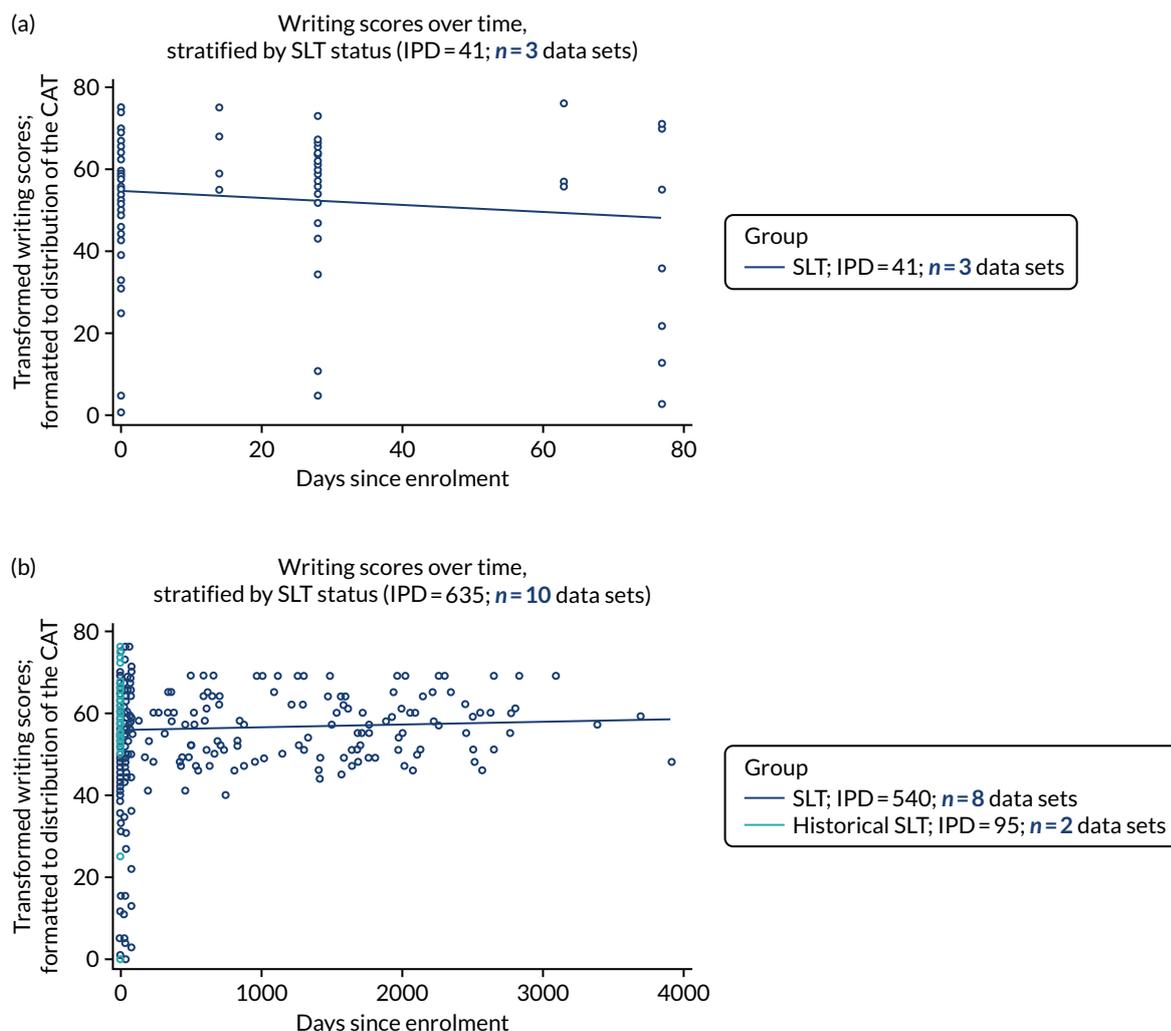


FIGURE 9 Writing scores over time. (a) RCTs; and (b) all study types.

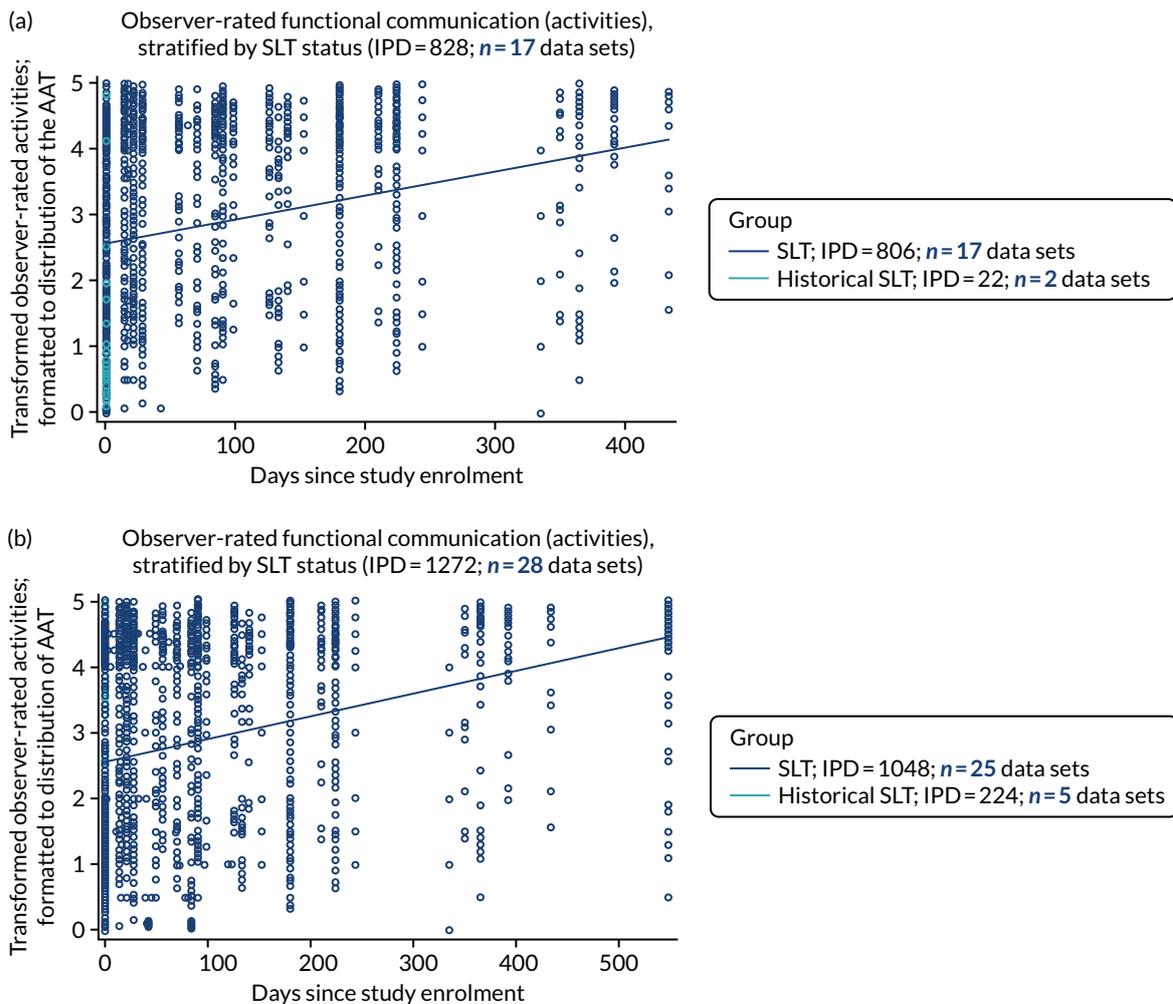


FIGURE 10 Observer-rated activity scores over time. (a) RCTs; and (b) all study types.

**Trajectory of self-rated functional communication (activity) over time**

Data were available on self-rated activity scores for 11 IPD (one RCT), and for 43 IPD (two data sets of all study types). The anchor measure for self-rated activity scores was the Assessment for Living with Aphasia (ALA). We observed an increase in self-rated activity scores with time (Figure 11) when using all study designs. Similar observations were seen for self-rated participation scores (see Report Supplementary Material 3, figure 2).

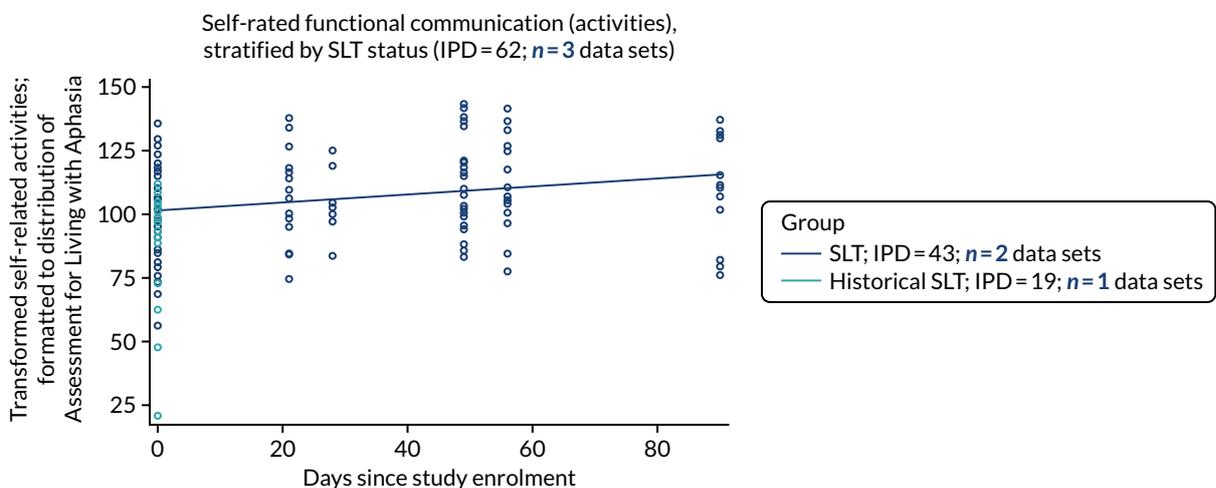


FIGURE 11 Self-rated activities over time in all study types.

## Distribution of language scores at study entry

We examined the distribution of participants' language scores for each domain, as measured at study entry. We selected this time point to mitigate any treatment effect due to access to study SLT. Scores gathered using minority measures were transformed to match the distribution of the relevant anchor measure for that language domain. We considered the distribution of language scores across all study entry time points (days since the index stroke for that study), first for RCT data sets, and then across all study designs. When data permitted, we also considered the distribution of scores within what collaborators agreed were clinically applicable time periods for typical enrolment in aphasia studies (0–1000 days since the index stroke).

### Overall language ability at study entry

Following transformation of overall language ability scores from minority measures to match the range of the WAB-AQ (anchor measure), we plotted language ability scores at study entry for RCT participants (700 IPD; 19 RCTs), and for all participants across all study designs for which overall language ability data were available (2571 IPD; 78 data sets).

Regression analyses based on data from the RCT population revealed that time since stroke at baseline (in months) was positively associated with better overall language ability (OR 1.010, 95% CI 1.006 to 1.014;  $p < 0.0001$ ) (see *Report Supplementary Material 3*, figure 3). We observed similar overall increasing language ability with increasing time since stroke among all participants across all study designs (OR 1.003, 95% CI 1.002 to 1.005;  $p < 0.0001$ ) (see *Report Supplementary Material 3*, figure 3).

When examining the distribution of overall language ability scores within more clinically applicable study enrolment time frames since index stroke (0–1000 days; 1780 IPD; 78 data sets), we observed a similar trend towards greater overall language ability with increasing time (in months) since stroke at baseline (OR 1.026, 95% CI 1.017 to 1.035;  $p < 0.0001$ ). A 1-year increase in time from stroke to study enrolment was associated with an improvement in overall language ability scores (OR 1.36, 95% CI 1.22 to 1.51;  $p < 0.0001$ ).

### Spontaneous recovery (overall language ability)

A further breakdown of overall language ability scores for study entry at 0–15, 15–30, 30–90, 90–180, 180–365 and 365–1095 days can be found in *Report Supplementary Material 3*; figures 4 (RCTs) and 5 (all study types). Spontaneous recovery within this domain could be most readily examined by looking at study entry between 0 and 90 days post index stroke, in adjunct with natural history data (which were not available). Examination of the distribution of overall language ability scores at study entry within this time period revealed relatively stable distributions as time increased from 0 to 30 days (45–50 points on the WAB-AQ). Scores appeared to plateau beyond 3–6 months (scores of between 60 and 70); however, this appears to be confounded by sparse data in this time period (see *Report Supplementary Material 3*, figures 4 and 5). Data should also be interpreted with caution, as scores at study entry (particularly beyond 15 days of index stroke) did not account for SLT exposure prior to study entry.

### Auditory comprehension at study entry

Auditory comprehension scores were transformed to fit the range of the anchor measure (the TT-AAT). We plotted these transformed scores at study entry for the RCT population (633 IPD; 19 RCTs; see *Report Supplementary Material 3*, figure 6) and across all study designs (2597 IPD; 67 data sets; see *Report Supplementary Material 3*, figure 6).

In the RCT population, auditory comprehension scores appeared to be stable with increased time to study entry. We examined whether or not the slope of the regression line was influenced by the small number of baseline data from later time points by examining the distribution within a more clinically applicable enrolment period of up to 1000 days since stroke in RCTs (506 IPD; 19 data sets; see *Report Supplementary Material 3*, figure 6). We observed a stable trend in auditory comprehension scores as time since stroke increased (see *Report Supplementary Material 3*, figure 6). This association was not significant when all baseline time to inclusion was considered (OR 1.001, 95% CI 0.996 to 1.005;  $p = 0.7312$ ) nor when time to inclusion was limited to 1000 days after stroke (OR 0.999, 95% CI 0.980 to 1.019;  $p = 0.9571$ ).

We then examined the distribution of auditory comprehension scores at increasing time to enrolment in all study types (see *Report Supplementary Material 3*, figure 6). In contrast to the RCT data set, we observed a slight increase in auditory comprehension scores at baseline with increasing time since stroke (2597 IPD; 67 data sets; see *Report Supplementary Material 3*, figure 6). Regression analysis showed no significant association between time to enrolment (in months) and auditory comprehension at baseline (OR 1.001, 95% CI 0.999 to 1.002;  $p = 0.3763$ ). We examined the distribution of baseline auditory comprehension scores further, looking at clinically applicable enrolment periods of 0–1000 days since stroke for all study types (1879 IPD; 66 data sets; see *Report Supplementary Material 3*, figure 6). There was no association between time since stroke at baseline (months) and auditory comprehension scores for the 0–1000 days since stroke (OR 1.008, 95% CI 0.999 to 1.017;  $p = 0.0863$ ).

### Spontaneous recovery (auditory comprehension)

A further breakdown of auditory comprehension scores for study entry at 0–15, 15–30, 30–90, 90–180, 180–365 and 365–1095 days can be found in *Report Supplementary Material 3*, figures 7 (RCTs) and 8 (all study types). Spontaneous recovery within this domain could be most readily examined by looking at study entry between 0 and 90 days post index stroke, in adjunct with natural history data (which were not available). Examination of the distribution of auditory comprehension scores at study entry within this time period (i.e. 0–90 days post index stroke) revealed higher scores between days 1 and 15 (ranging between 27 and 28 points on the TT-AAT), and diminishing with time up to 3 months (ranging between 15 and 18 points on the TT between 1 and 3 months). However, this observation appears to be confounded by sparse data within this time period (see *Report Supplementary Material 3*, figure 7) and the fact that data did not account for SLT exposure prior to study entry, particularly for enrolment beyond 15 days of stroke.

### Naming scores at study entry

We described the distribution of naming scores at study entry in RCTs (748 IPD; 25 RCTs; see *Report Supplementary Material 3*, figure 9) and all study designs (2760 IPD; 72 data sets; see *Report Supplementary Material 3*, figure 9). In the RCT population, naming scores appeared to be stable with increasing time from stroke to study entry (OR 1.00, 95% CI 0.996 to 1.003;  $p = 0.95$ ). In contrast, for all study designs, an increase in baseline time (in months) was associated with increased naming scores (OR 1.005, 95% CI 1.004 to 1.007;  $p < 0.0001$ ). A similar trend towards better naming scores with increased time from stroke to study enrolment (months) was observed within a clinically applicable period of 0–1000 days (1836 IPD; 71 data sets; see *Report Supplementary Material 3*, figures 9–11) (OR 1.031, 95% CI 1.022 to 1.040;  $p \leq 0.0001$ ).

### Spontaneous recovery (naming)

A further breakdown of naming scores for study entry at 0–15, 15–30, 30–90, 90–180, 180–365 and 365–1095 days can be found in *Report Supplementary Material 3*, figures 10 (RCTs) and 11 (all study types). Spontaneous recovery within this domain could be most readily examined by looking at study entry between 0 and 90 days post index stroke, in adjunct with natural history data (which were not available). Examination of the distribution of naming scores at study entry within this time period

(i.e. 0–90 days post index stroke) revealed higher scores between days 1 and 15 (ranging between 10 and 22 points on the BNT), and diminishing with time after 3 months (ranging between 7 and 12 points on the BNT between 1 and 3 months). However, this observation appears to be confounded by sparse data within this time period (see *Report Supplementary Material 3*, figures 10 and 11) and the fact that data did not account for SLT exposure prior to study entry.

### **Other spoken language at study entry**

We described the distribution of other spoken-language scores at study entry for participants who were enrolled in a RCT (163 IPD; 2 RCTs; see *Report Supplementary Material 3*, figure 12) and across all study designs (344 IPD; 7 data sets; see *Report Supplementary Material 3*, figure 12). We observed relatively stable spoken-language scores among the RCT population as study entry time increased (OR 0.999, 95% CI 0.992 to 1.005;  $p = 0.69$ ). There appeared to be relatively stable spoken-language scores with increasing time to study enrolment among participants from all study types (OR 1.002, 95% CI 0.998 to 1.007;  $p = 0.26$ ) (see *Report Supplementary Material 3*, figure 12). Similar patterns were observed when examining a clinically applicable study enrolment period (0–1000 days; see *Report Supplementary Material 3*, figure 12).

### **Reading comprehension at study entry**

We plotted the distribution of reading comprehension scores at study entry. These scores were transformed to fit the range of the CAT reading comprehension subtest. Data from the RCT population were available for only 11 IPD from one RCT, and therefore did not meet our prerequisites for analysis. We examined data at study entry from all study types (652 IPD; 9 data sets; see *Report Supplementary Material 3*, figure 13). We observed stable reading scores over time from stroke to study enrolment (OR 1.001, 95% CI 0.999 to 1.003;  $p = 0.46$ ). We examined the distribution of scores during a more clinically applicable time span of 0–1000 days (see *Report Supplementary Material 3*, figure 13). We observed similarly stable reading comprehension scores among participants recruited later after stroke onset (OR 0.996, 95% CI 0.978 to 1.014;  $p = 0.68$ ).

### **Writing at study entry**

Randomised controlled trial data on writing scores at study entry were available for only 11 IPD from one RCT, and were therefore not taken forward for further analysis. Data on 673 IPD (11 data sets; see *Report Supplementary Material 3*, figure 14) were available across all study types. Writing scores appeared to increase slightly with increasing time to study enrolment, but this was not significant (OR 1.000, 95% CI 0.998 to 1.002;  $p = 0.96$ ), nor was it significant within a more clinically applicable period of 0–1000 days (421 IPD; 11 data sets; see *Report Supplementary Material 3*, figure 14) (OR 1.003, 95% CI 0.986 to 1.021;  $p = 0.71$ ).

### **Observer-rated functional communication (activity) at study entry**

Data on observer-rated functional communication (activity) were converted to match the range of the AAT-SSC domain. Data were available for 998 IPD from 18 RCTs. We observed stable activity scores with increasing time to inclusion in RCTs (see *Report Supplementary Material 3*, figure 15) (OR 0.999, 95% CI 0.994 to 1.003;  $p = 0.51$ ). We observed increased activity scores with increasing time to enrolment in RCTs when examining a more clinically applicable time period (0–1000 days after stroke; see *Report Supplementary Material 3*, figure 15) (OR 1.021; 95% CI 1.001 to 1.042;  $p = 0.036$ ).

Data were available on activity measures for 1437 IPD from 29 data sets across all study types (see *Report Supplementary Material 3*, figure 15). We observed relatively stable activity scores with increasing time from stroke to study enrolment (OR 1.0; 95% CI 0.997 to 1.003;  $p = 0.94$ ). Within a clinically meaningful enrolment period (0–1000 days after stroke), we observed similarly stable scores with increasing time to study enrolment (OR 1.005, 95% CI 0.992 to 1.019;  $p = 0.46$ ) (see *Report Supplementary Material 3*, figure 15).

Observer-rated participation data were derived from this data set and also demonstrated similar observations across RCTs and all study types (see *Report Supplementary Material 3*, figure 16). A further breakdown of language ability scores for study entry at 0–15, 15–30, 30–90, 90–180, 180–365 and 365–1095 days can be found in *Report Supplementary Material 3*, figure 17 (RCTs) and 18 (all study types).

### **Spontaneous recovery [observer-rated functional communication (activity)]**

Spontaneous recovery within this domain could be most readily examined by looking at study entry between 0 and 90 days post index stroke, in adjunct with natural history data (which were not available). Examination of the distribution of observer-rated activity scores at study entry within this time period (i.e. 0–90 days post index stroke) revealed higher scores between days 1 and 30 (ranging between 1.5 and 2.5 points on the AAT-SSC), and stabilising with time after 3 months (ranging between 2 and 2.5 points on the AAT-SSC). However, this observation appears to be confounded by sparse data within this time period (see *Report Supplementary Material 3*, figures 16 and 17) and the fact that data did not account for SLT exposure prior to study entry.

### **Observed-rated functional communication (participation) at study entry**

Observer-rated participation data were also derived from this data set and also demonstrated similar observations across RCTs and all study types (see *Report Supplementary Material 3*, figure 18).

### **Self-rated functional communication at baseline**

Data were available for only 11 IPD from one RCT on self-rated activity and participation. Data were therefore examined from all study types (see *Report Supplementary Material 3*, figure 19). Across all baseline times to study inclusion, self-rated activity scores appeared stable (OR 1.004, 95% CI 0.993 to 1.014;  $p = 0.48$ ). This was also apparent when examining a more clinically meaningful enrolment period of 0–1000 days (OR 0.991, 95% CI 0.914 to 1.075;  $p = 0.83$ ). Data on self-rated participation were also generated from these IPD and showed similar distributions (see *Report Supplementary Material 3*, figure 20).

## **Language recovery: absolute proportion of change in language scores from baseline to first follow-up after access to speech and language therapy**

We examined the median absolute proportion of change observed across each language domain from baseline to the first follow-up after SLT. *Chapter 7* details dichotomised sensitivity analyses that take into account recovery in participants relative to their initial language impairment.

The absolute proportion of change was calculated independently from the transformed scores and the maximum possible score on the relevant anchor measure. Data were presented in absolute percentages, so as to compare recovery across each domain. We first considered data extracted from RCTs (*Figure 12a*) followed by data extracted across all study types, regardless of study design (see *Figure 12b*). Figures are presented as medians and IQRs.

We identified suitable data on measures of overall language ability (418 IPD; 11 RCTs), auditory comprehension (508 IPD; 17 RCTs), naming (346 IPD; 14 RCTs), other spoken language (155 IPD; 2 RCTs), reading (11 IPD; 1 RCT), writing (41 IPD; 3 RCTs) and functional communication (activity and participation) (608 IPD; 16 RCTs). For participants who had access to SLT in a RCT, we observed the greatest median percentage changes since baseline in observer-rated activity scores (10%) and overall language ability scores (8.4%), followed by auditory comprehension (8.0%).

We then considered the wider data set, inclusive of participants from all study designs. We identified suitable data on overall language ability (788 IPD; 21 data sets), auditory comprehension (921 IPD; 27 data sets), naming (646 IPD; 24 data sets), spoken language (204 IPD; 5 data sets), reading scores

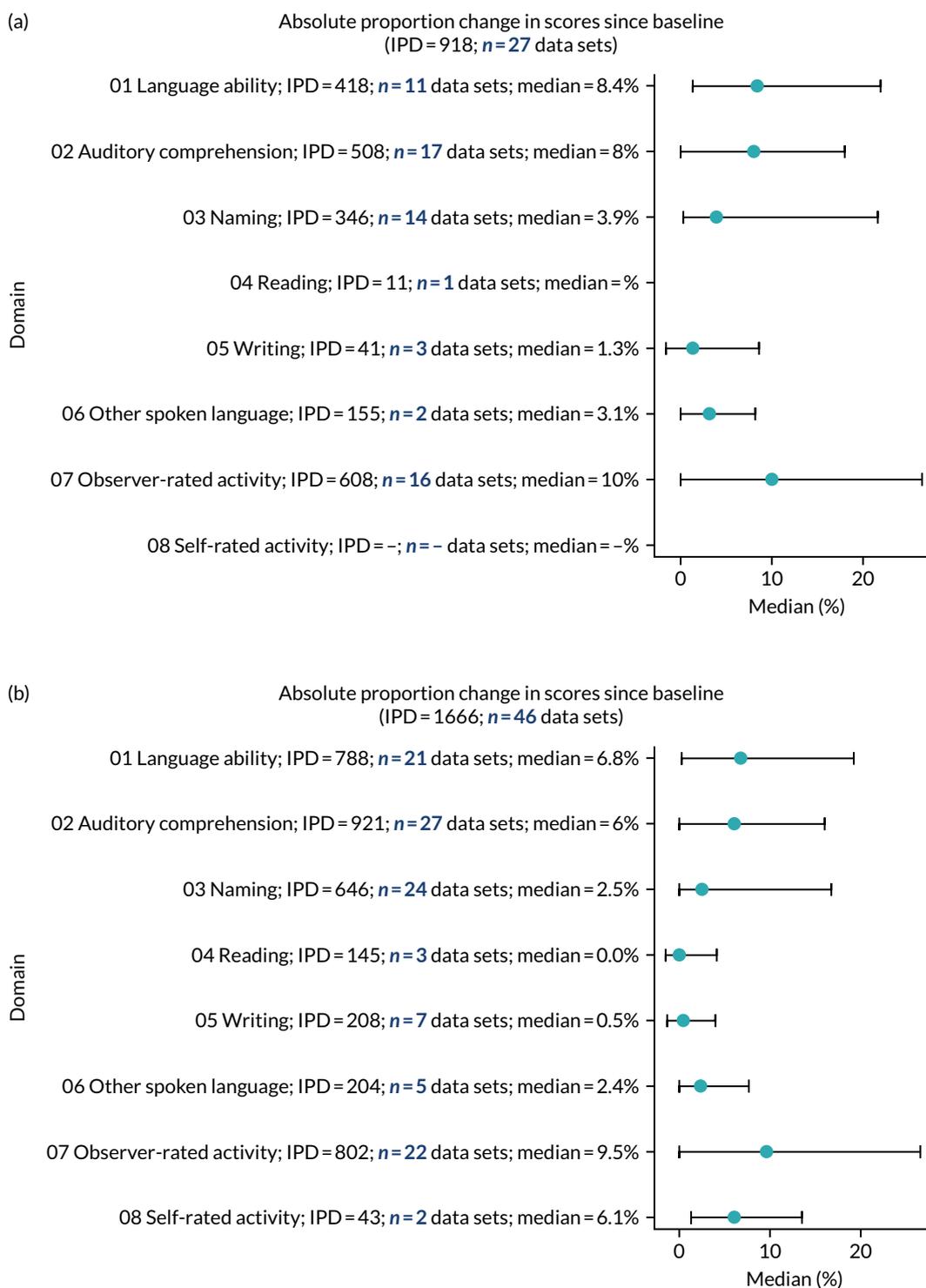


FIGURE 12 Absolute proportion of change (median and IQR) in domain scores between baseline to first follow-up. (a) RCTS; and (b) all study types.

(145 IPD; 3 data sets), writing measures (208 IPD; 7 data sets) and functional communication (observer-rated activity: 802 IPD from 22 data sets; self-rated activity: 43 IPD from 2 datasets; see Figure 12). Participants allocated to SLT had the highest median percentage change since baseline in observer-rated functional communication activity scores (9.5%), followed by overall language ability (6.8%) and auditory comprehension (6%) (see Figure 12).

## Change in domain scores stratified by time to enrolment

We explored the role that time since index stroke and study enrolment played on the proportion of recovery observed for each domain score. Time since stroke at inclusion in the primary data set was stratified into the following groupings:

- 0–1 month
- > 1–3 months
- > 3–6 months
- > 6 months following index stroke.

There were no participants in the no-SLT group (those who received only historical SLT) for whom values were available at the first follow-up period (in order to calculate change in language domain scores from baseline). Although data were available at later follow-up time points for this population, in the interim period SLT had been administered. This meant that there was no way to ascertain accurately the impact of no SLT on changes in language domain scores from baseline. Results are therefore presented for participants who had access to SLT, for RCTs (Figure 13) and across all study types (see Report Supplementary Material 3, figure 21). As the distribution of data within each domain were skewed, we presented data on the medians and IQRs for each time point.

### Recovery in the randomised controlled trial population

#### Overall language ability

In those enrolled within 1 month of stroke, the median change in overall language ability score was 16.7% (207 IPD; 10 data sets). This median change since baseline decreased for those enrolled between > 1 and 3 months of index stroke (median 9.5%; 48 IPD; 6 data sets), those enrolled between > 3 and 6 months of index stroke (median 5%; 20 IPD; 4 data sets) and those enrolled beyond 6 months of stroke (median 4.2%; 143 IPD; 4 data sets). The largest proportion of change in overall language ability scores was seen in those who were enrolled within 1 month of index stroke (see Figure 13a).

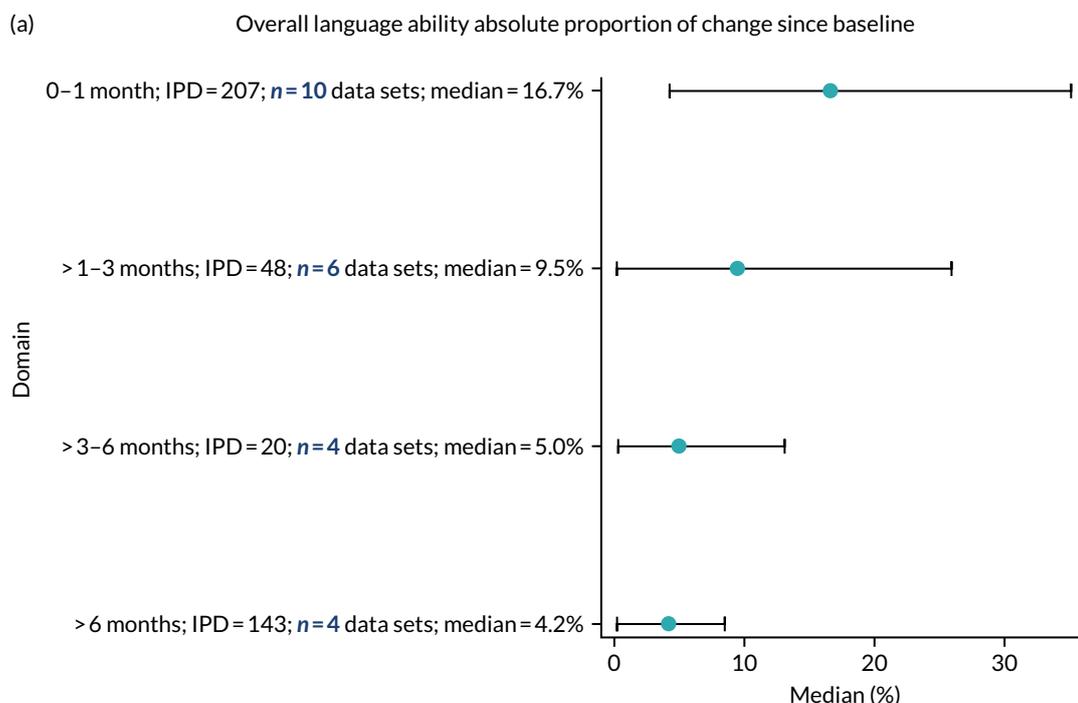


FIGURE 13 Proportion of recovery (median and IQR) across all language domains, stratified by time to study entry across RCTs. (a) Overall language ability; (b) auditory comprehension; (c) naming; (d) other spoken language; (e) writing; (f) observer-rated activities; and (g) observer-rated participation. (continued)

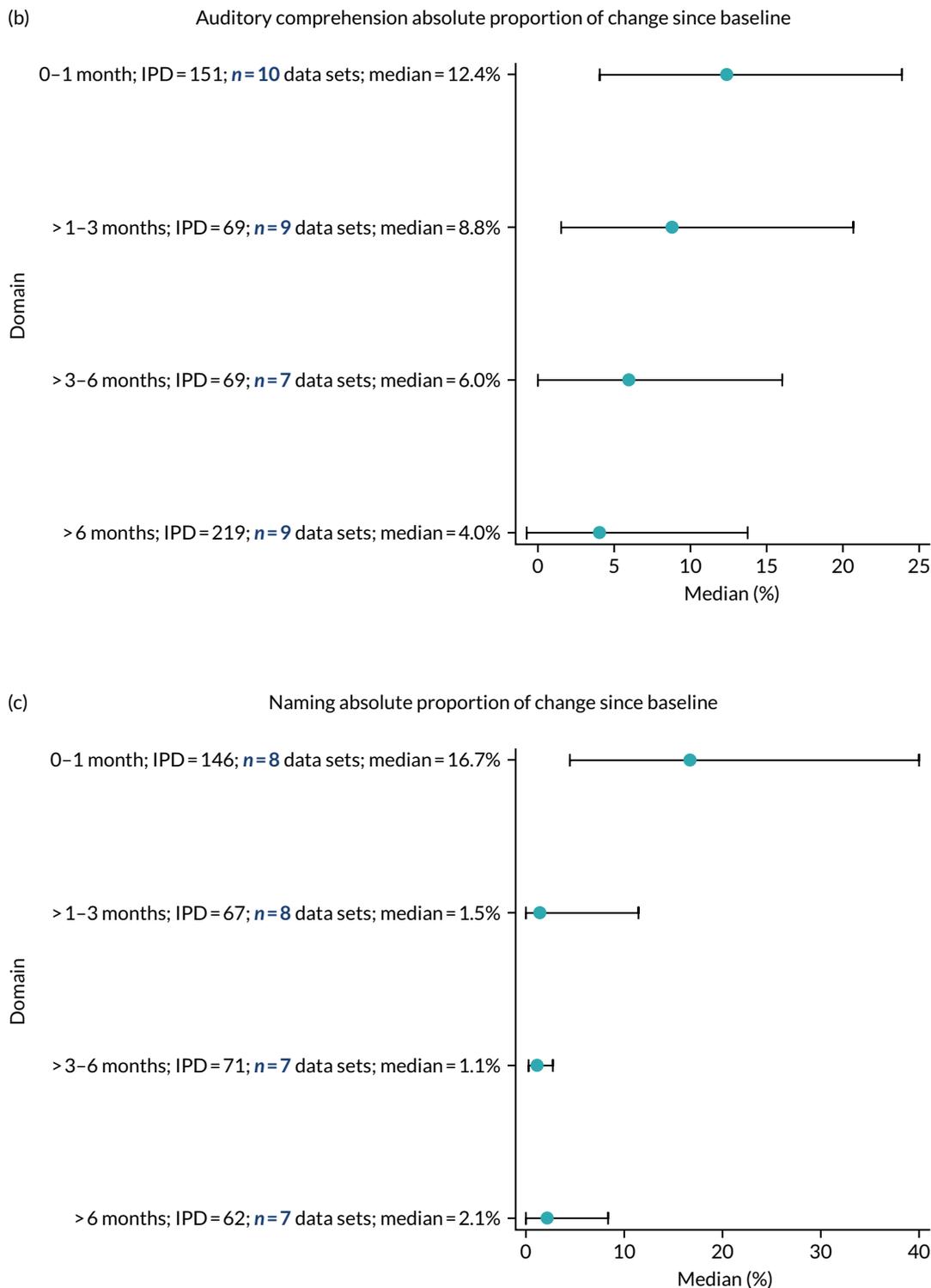


FIGURE 13 Proportion of recovery (median and IQR) across all language domains, stratified by time to study entry across RCTs. (a) Overall language ability; (b) auditory comprehension; (c) naming; (d) other spoken language; (e) writing; (f) observer-rated activities; and (g) observer-rated participation. (*continued*)

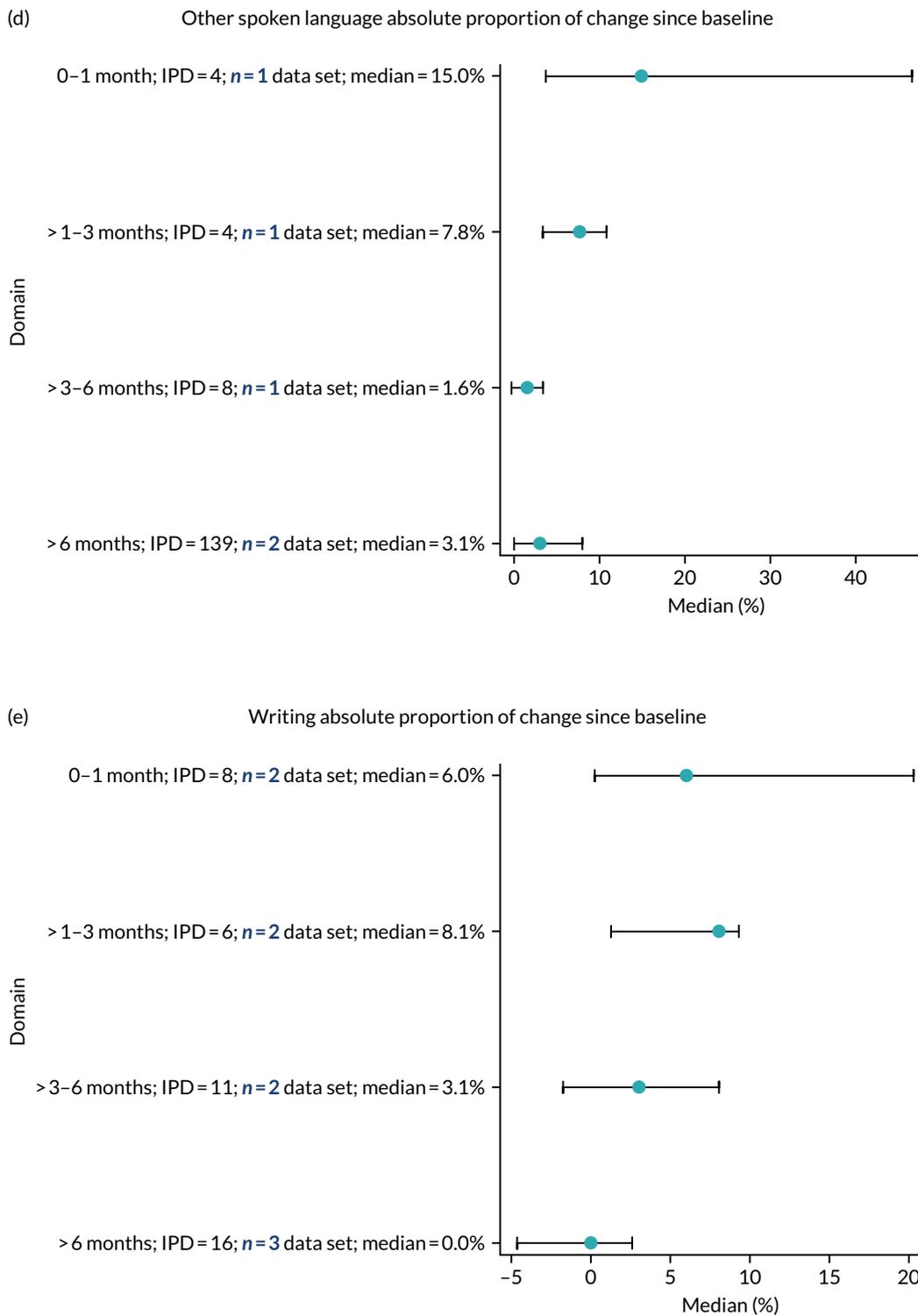


FIGURE 13 Proportion of recovery (median and IQR) across all language domains, stratified by time to study entry across RCTs. (a) Overall language ability; (b) auditory comprehension; (c) naming; (d) other spoken language; (e) writing; (f) observer-rated activities; and (g) observer-rated participation. (continued)

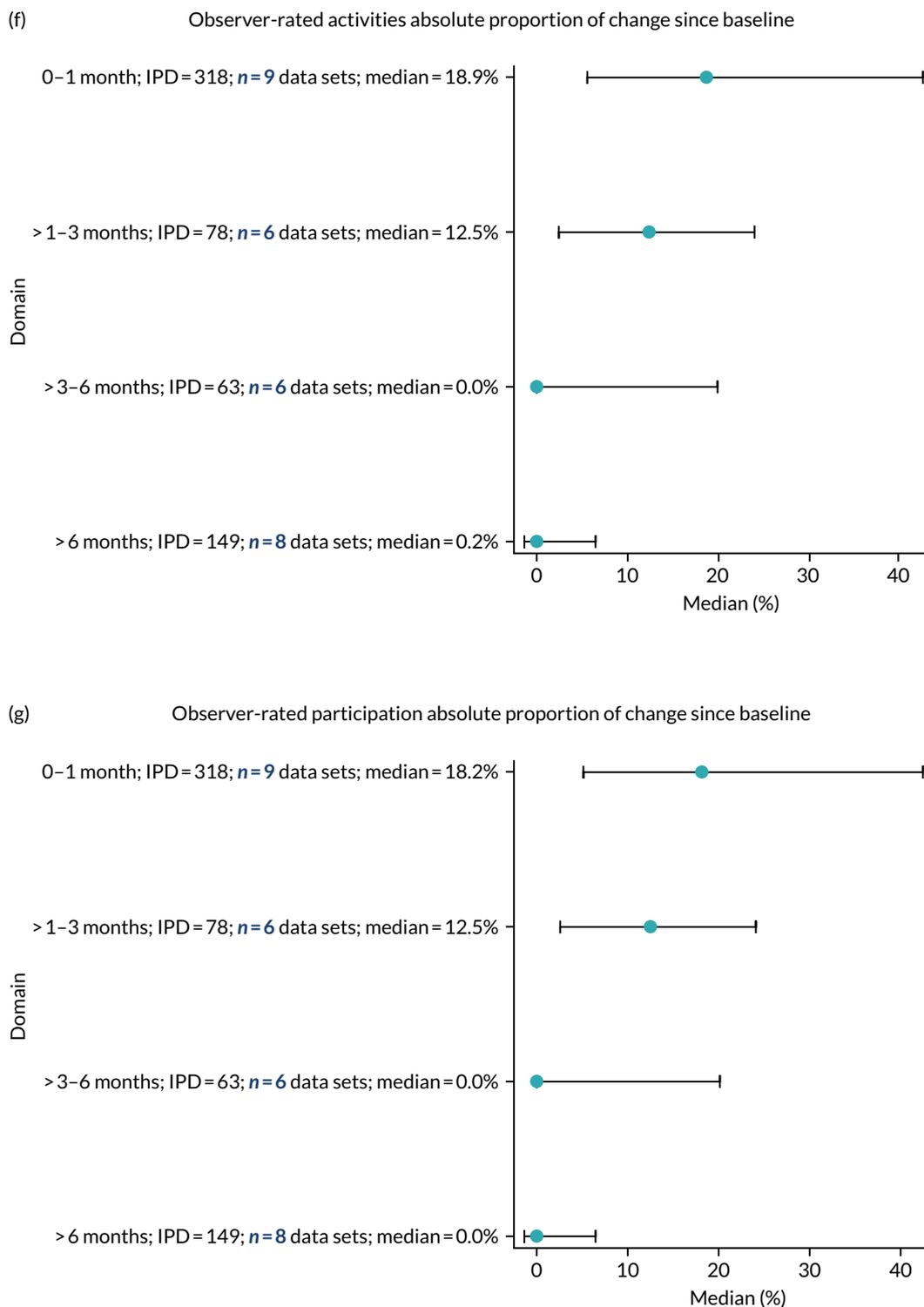


FIGURE 13 Proportion of recovery (median and IQR) across all language domains, stratified by time to study entry across RCTs. (a) Overall language ability; (b) auditory comprehension; (c) naming; (d) other spoken language; (e) writing; (f) observer-rated activities; and (g) observer-rated participation.

### **Auditory comprehension**

For those enrolled within 1 month of stroke, the median change in auditory comprehension score was 12.4% (151 IPD; 10 data sets). This decreased to 8.8% for those who were enrolled between > 1 and 3 months of index stroke (69 IPD; 9 data sets), to 6% for those enrolled between > 3 and 6 months of stroke (69 IPD; 7 data sets) and to 4% for those enrolled after 6 months of index stroke (219 IPD; 9 data sets). The largest proportion of change in auditory comprehension scores was seen in those who were enrolled within 1 month of index stroke (see *Figure 13b*).

### **Naming**

For those enrolled within 1 month of stroke, the median change in naming score was 16.7% (146 IPD; 8 data sets). For those enrolled between > 1 and 3 months of stroke, the median change was 1.5% (67 IPD; 8 data sets). For participants enrolled between > 3 and 6 months of stroke, the median change in naming score had decreased to 1.1% (71 IPD; 7 data sets); for those enrolled beyond 6 months of index stroke, the median change was 2.1% (62 IPD; 7 data sets). The largest changes in naming scores were seen in those enrolled within the first month of index stroke (see *Figure 13c*).

### **Other spoken language**

There were inadequate data for a reliable description of median change in other spoken-language score within 1 month of stroke (4 IPD; 1 data set), between > 1 and 3 months of stroke (4 IPD; 1 data set) and between > 3 and 6 months of stroke (8 IPD; 1 data set). For those enrolled beyond 6 months of stroke, the median change was 3.1% (139 IPD; 2 data sets). These data should be interpreted with caution as the IPD at each time point were very small (see *Figure 13d*).

### **Reading comprehension**

Data on changes in reading comprehension scores were not available for participants enrolled at 0–1 months, > 1–3 months or > 3–6 months after stroke. Data for those enrolled in a study > 6 months after index stroke could not be analysed as they did not meet our prespecified minimum data set requirement for analysis (11 IPD; 1 data set).

### **Writing**

For those enrolled within 1 month of stroke, the median change in writing score was 6% (8 IPD; 2 data sets). For those enrolled between > 1 and 3 months of stroke, the median change was 8.1% (6 IPD; 2 data sets); for enrolment between > 3 and 6 months of stroke, this had decreased to 3.1% (11 IPD; 2 data sets), and in those enrolled beyond 6 months of stroke, the median change was 0% (16 IPD; 3 data sets). There were inadequate data for clinically meaningful analyses (see *Figure 13e*).

### **Observer-rated functional communication (activity)**

Within an enrolment period of 0–1 months of the index stroke, the median percentage change in observer-rated functional communication (activity) was 18.9% (318 IPD; 9 data sets). At > 1–3 months of enrolment, it was 12.5% (78 IPD; 6 data sets); at > 3–6 months, it was 0% (63 IPD; 6 data sets); and by > 6 months, it was 0.2% (149 IPD; 8 data sets). The highest proportion of change was seen for earlier time points (see *Figure 13f*).

### **Observer-rated functional communication (participation)**

There were 318 IPD from nine data sets on functional communication (participation) for study entry between 0 and 1 month after index stroke (median change 18.2%). The median change in participation at > 1–3 months was 12.5% (78 IPD; 6 data sets); at > 3–6 months, it was 0% (63 IPD; 6 data sets); and by > 6 months it was 0% (149 IPD; 8 data sets). The highest proportion of change was seen for earlier time points (see *Figure 13g*).

### **Self-rated functional communication**

Data were available at only > 6 months for self-rated functional communication, thereby precluding any further analyses.

## Recovery in all study types

### Overall language ability

For those enrolled within 1 month of stroke, the median change in overall language ability score was 16.3% (389 IPD; 15 data sets). This median change since baseline decreased for those enrolled between > 1 and 3 months of index stroke (median 8.6%; 57 IPD; 9 data sets), for those enrolled between > 3 and 6 months of index stroke (median 1.5%; 30 IPD; 7 data sets) and for those enrolled beyond 6 months of stroke (median 2.2%; 312 IPD; 11 data sets). The largest proportion of change in overall language ability scores was seen in those enrolled within 1 month of index stroke (see *Report Supplementary Material 3*, figure 21).

### Auditory comprehension

For those enrolled within 1 month of stroke, the median change in auditory comprehension score was 10% (339 IPD; 14 data sets); this similar to the change for those enrolled between > 1 and 3 months of index stroke (median 8.8%; 80 IPD; 11 data sets). The median change had decreased for those enrolled between > 3 and 6 months of stroke (median 4%; 82 IPD; 10 data sets) and for those enrolled beyond 6 months of stroke (median 2.7%; 420 IPD; 16 data sets). The largest proportion of change in auditory comprehension scores was seen in those enrolled within 1 month of index stroke (see *Report Supplementary Material 3*, figure 21).

### Naming

For those enrolled within 1 month of stroke, the median change in naming score was 8.3% (198 IPD; 10 data sets). For those enrolled between > 1 and 3 months of stroke, the median change was 1.9% (77 IPD; 10 data sets); for participants enrolled between > 3 and 6 months of stroke, this decreased to 0.9% (84 IPD; 10 data sets). For those enrolled beyond 6 months of stroke, the median change in naming scores was 1.9% (287 IPD; 16 data sets). The largest changes in naming scores were seen in those enrolled within 1 month of index stroke (see *Report Supplementary Material 3*, figure 21).

### Other spoken language

There were inadequate data for a reliable description of median change in other spoken-language score for those enrolled within 1 month of stroke (6 IPD; 2 data sets), and for those enrolled between > 1 and 3 months of stroke (7 IPD; 2 data sets). For those enrolled within between > 3 and 6 months of stroke, the median change was 1.9% (13 IPD; 2 data sets), and for those enrolled beyond 6 months of stroke, the median change was 2.4% (178 IPD; 5 data sets). Proportion of change in other spoken-language scores increased very slightly from > 3–6 months to beyond 6 months. However, these data should be interpreted with caution as the IPD available at each time point were very small (see *Report Supplementary Material 3*, figure 21).

### Reading comprehension

Data on reading comprehension were not available for participants enrolled between 0 and 1 month of stroke; for those who were enrolled in a study between > 1–3 months and > 3–6 months of stroke, only six IPD were available. By > 6 months of index stroke, the median change in scores at final follow-up was 0% (133 IPD; 3 data sets).

### Writing

For those enrolled within 1 month of stroke, the median change in writing score was 9.1 (10 IPD; 3 data sets). For those enrolled between > 1 and 3 months of stroke, the median change was 3.9% (13 IPD; 4 data sets); for those enrolled between > 3 and 6 months of stroke, this decreased to 2.1% (21 IPD; 4 data sets), and for those enrolled beyond 6 months of stroke, it was 0% (164 IPD; 7 data sets). Larger changes in writing scores were seen in those enrolled within 0–1 month after index stroke (see *Report Supplementary Material 3*, figure 21).

**Observer-rated functional communication (activity)**

Within an enrolment period of 0–1 month after the index stroke, the median percentage change for observer-rated functional communication (activity) was 16.2% (442 IPD; 11 data sets). The median change in activity for those enrolled within > 1–3 months of stroke was 12.5% (80 IPD; 7 data sets); for those enrolled within > 3–6 months, it was 0% (64 IPD; 7 data sets), and for those enrolled beyond 6 months, it was 1.1% (216 IPD; 12 data sets). The highest proportion of change was seen for earlier time points (see *Report Supplementary Material 3*, figure 21).

**Observer-rated functional communication (participation)**

There were 397 IPD from 10 data sets on observer-rated functional communication (participation) for study entry within 0–1 month after index stroke (median change 16.3%). The median change in activity for those enrolled between > 1 and 3 months of stroke was 12.5% (78 IPD; 6 data sets); for those enrolled between > 3 and 6 months, it was 0% (64 IPD; 7 data sets), and for those enrolled beyond 6 months, it was 0.6% (216 IPD; 12 data sets). The highest proportion of change was seen for earlier time points (see *Report Supplementary Material 3*, figure 21).

**Self-rated functional communication**

Data were available at only > 6 months for self-rated functional communication, thereby precluding any further analyses.

**Summary**

There were insufficient data with which to ascertain the natural history of language impairment progression following aphasia due to stroke. Many data sets in which participants were allocated to the no-SLT group (historical SLT only) were permitted to receive SLT following completion of the study intervention period. Coupled with sparse post-intervention assessment time points, this limited the data available for the natural history analyses.

Similarly, we could not compare the trajectory of language scores over time for historical SLT with that for SLT-treated populations. Data in the historical comparison group were either available at baseline only, did not have a corresponding post-intervention follow-up value or did not meet our minimum eligibility criteria for the analysis. For those who had access to SLT, we observed an improvement in scores over time. This was less pronounced for 'other spoken-language production.'

Examining the scores for each language domain at study entry for all study types suggested better scores with increased time to study enrolment. However, these were only significant for overall language ability and naming.

The median proportion of change was selected to describe the change since baseline across all domains, as it was a more accurate reflection of the distribution of the skewed populations across each language domain. The greatest proportion of change was seen in the domains of observer-rated functional communication (10.0%) and overall language ability (8.4%), followed by auditory comprehension (8.0%), although the CIs were wide for each of these domains, and overlapped. For each of our analyses, similar results were observed whether examining the RCT population alone or all study types. The proportion of change in each domain score since baseline appeared to decrease with increasing time since index stroke. Although many of these differences since baseline did not appear to be significantly different across different domains (e.g. the 95% CIs overlapped), the proportions were notable from a clinical standpoint for some domains (e.g. 16.7% change on the WAB-AQ from baseline for overall language ability; 18.9% change in AAT-SSC for observer-rated activities), and were therefore presented.

# Chapter 5 Predictors of language recovery

## Overview

In this chapter, we explore the distribution of language data at study entry according to key demographic factors (age, sex and living context). We then examine the relationship between key demographic factors and absolute proportion of recovery at follow-up for each language domain. Finally, we examine predictors of language recovery following aphasia after stroke; this was done by undertaking a series of meta-analyses on selected subsets of the IPD. We used a one-stage approach, simultaneously analysing all relevant IPD from the entire database, and included the individual study as a random effect in all analyses.

We examined both significance and the absolute change in raw scores. Analyses could reveal non-significant results with notable effect sizes from a clinical perspective. We therefore reported on significant as well as non-significant results, when a notable clinical effect size existed.

## Language performance at study entry, stratified by age

We described language performance on each language domain for participants on study entry (baseline assessment). This time point was selected as no study intervention had yet been administered, and data were available for pre-intervention assessments across a range of time points since aphasia onset, thereby providing an indication of the distribution of language domain scores across different time points since the index stroke.

### Age and overall language ability at baseline

We examined the distribution of overall language ability in RCTs (700 IPD; 19 RCTs; *Figure 14a*), stratified by four age groups:  $\leq 55$  years (209 IPD; 19 data sets), 56–65 years (204 IPD; 19 data sets), 66–75 years (149 IPD; 18 data sets) and aged 75+ years (138 IPD; 13 data sets). As time to inclusion increased, so too did baseline language ability scores across all age strata. When examining a clinically meaningful enrolment period (0–1000 days post stroke; see *Figure 14c*), the CIs for all age groups appeared to overlap, indicating that these differences were not significant.

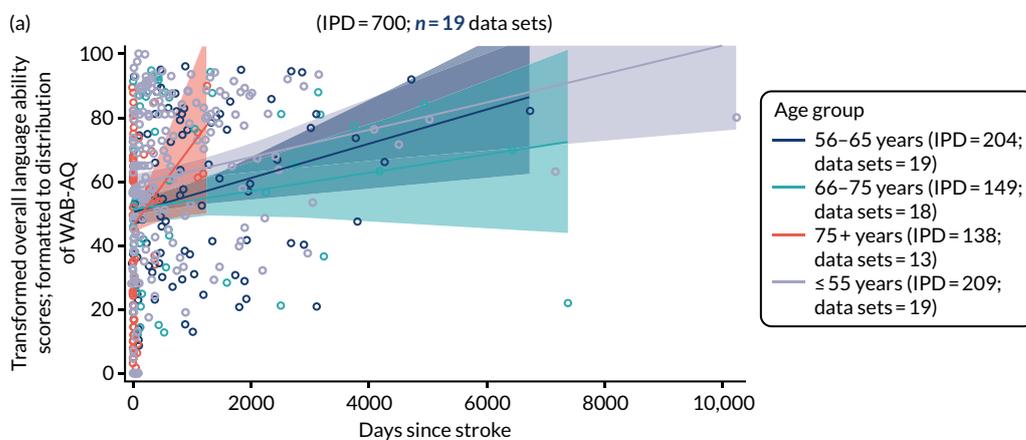


FIGURE 14 Overall language ability scores by age for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

## PREDICTORS OF LANGUAGE RECOVERY

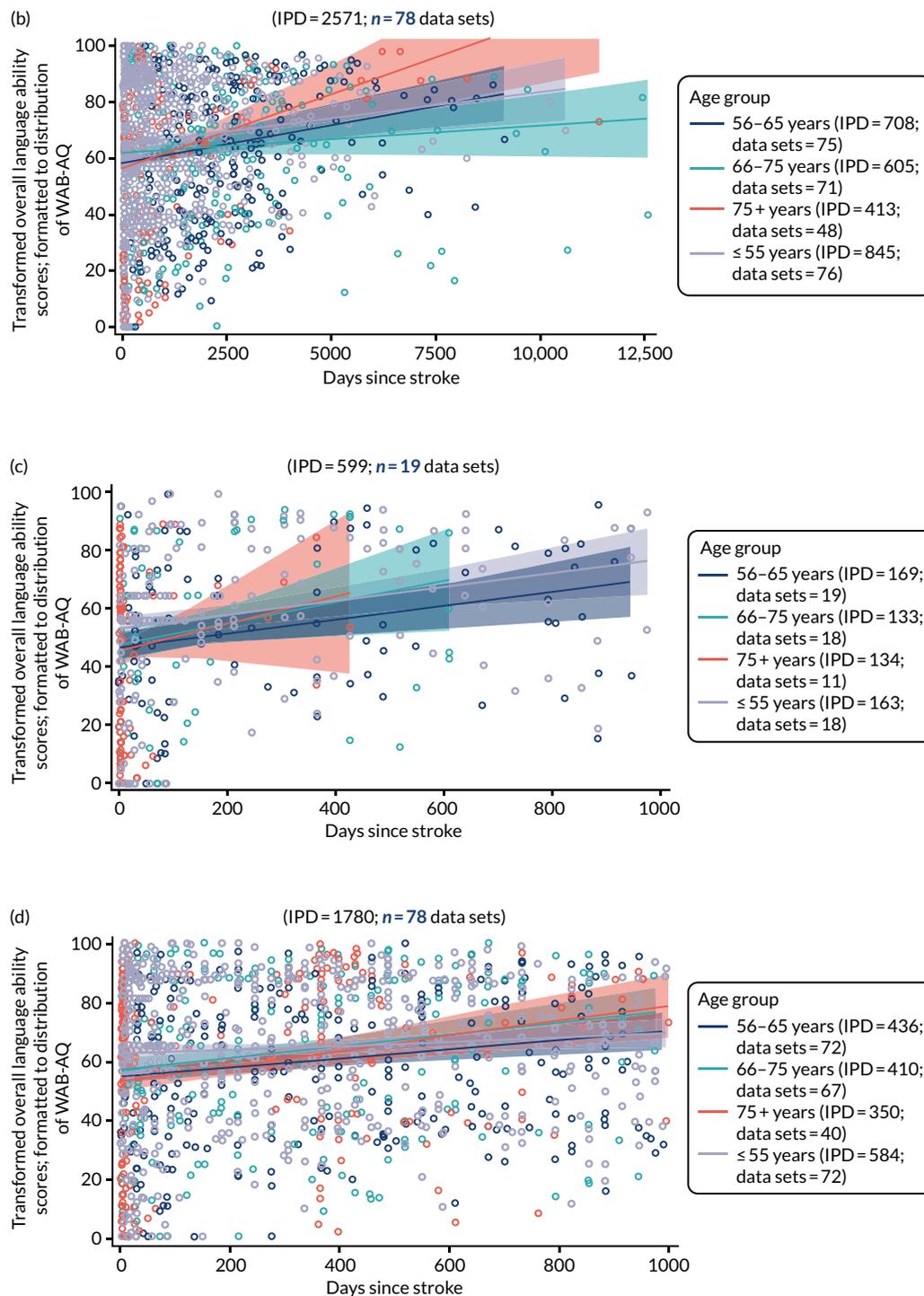
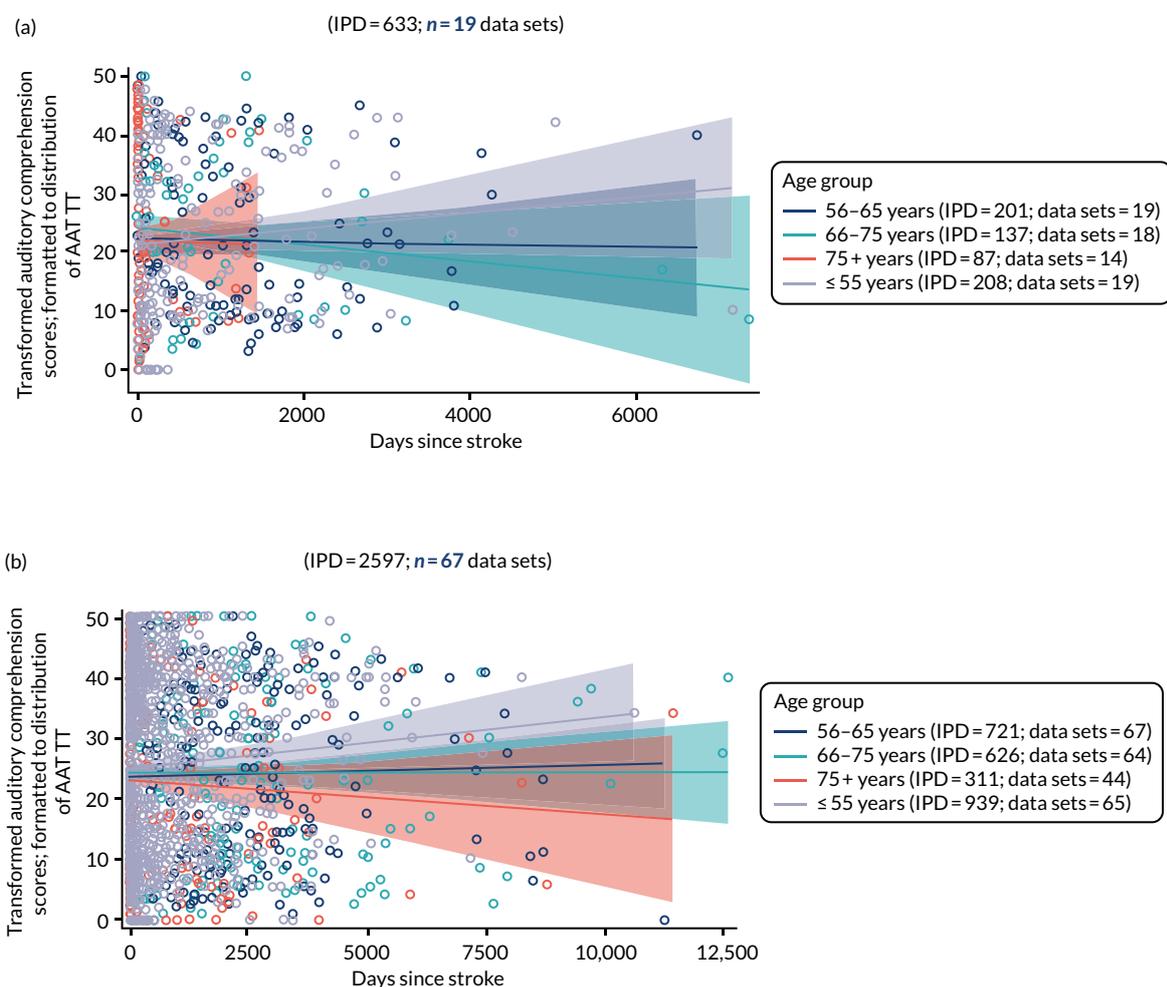


FIGURE 14 Overall language ability scores by age for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

We then examined overall language ability at baseline for participants in all study types (2571 IPD; 78 data sets; see Figure 14b). Data were available for the following age groups: ≤ 55 years (845 IPD; 76 data sets), 56–65 years (708 IPD; 75 data sets), 66–75 years (605 IPD; 71 data sets) and 75+ years (413 IPD; 48 data sets). All age groups appeared to have increased overall language ability scores as time since stroke at baseline increased. We examined overall severity scores up to 1000 days after stroke onset to reflect typical trial recruitment periods after index stroke (see Figure 14c and 14d). For participants recruited within 1000 days of index stroke, the confidence limits for each age group overlapped, indicating no difference in the distributions of overall language ability scores by age in all study types.

### Age and auditory comprehension at baseline

We examined the distribution of auditory comprehension scores at different baseline time points, stratified by age (633 IPD; 19 RCTs; *Figure 15a*). Data were available on participants aged  $\leq 55$  years (208 IPD; 19 RCTs), 56–65 years (201 IPD; 19 RCTs), 66–75 years (137 IPD; 18 RCTs) and  $> 75$  years (87 IPD; 14 RCTs). The confidence limits overlapped for each age stratum, indicating that there was no evidence of a difference in distributions of auditory comprehension scores across each age group (see *Figure 15a*), with similar findings for the data from all study designs (2597 IPD; 67 data sets; see *Figure 15b*). Across all study designs, data on auditory comprehension scores at baseline were available for participants aged  $\leq 55$  years (939 IPD; 65 data sets), 56–65 years (721 IPD; 67 data sets), 66–75 years (626 IPD; 64 data sets) and  $> 75$  years (311 IPD; 44 data sets). When we examined data for enrolment within 1000 days of index stroke (see *Figure 15c* and *d*), we observed similar overlaps in auditory comprehension scores across each age stratum, indicating no significant difference in the scores across different age groups.



**FIGURE 15** Auditory comprehension scores by age for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

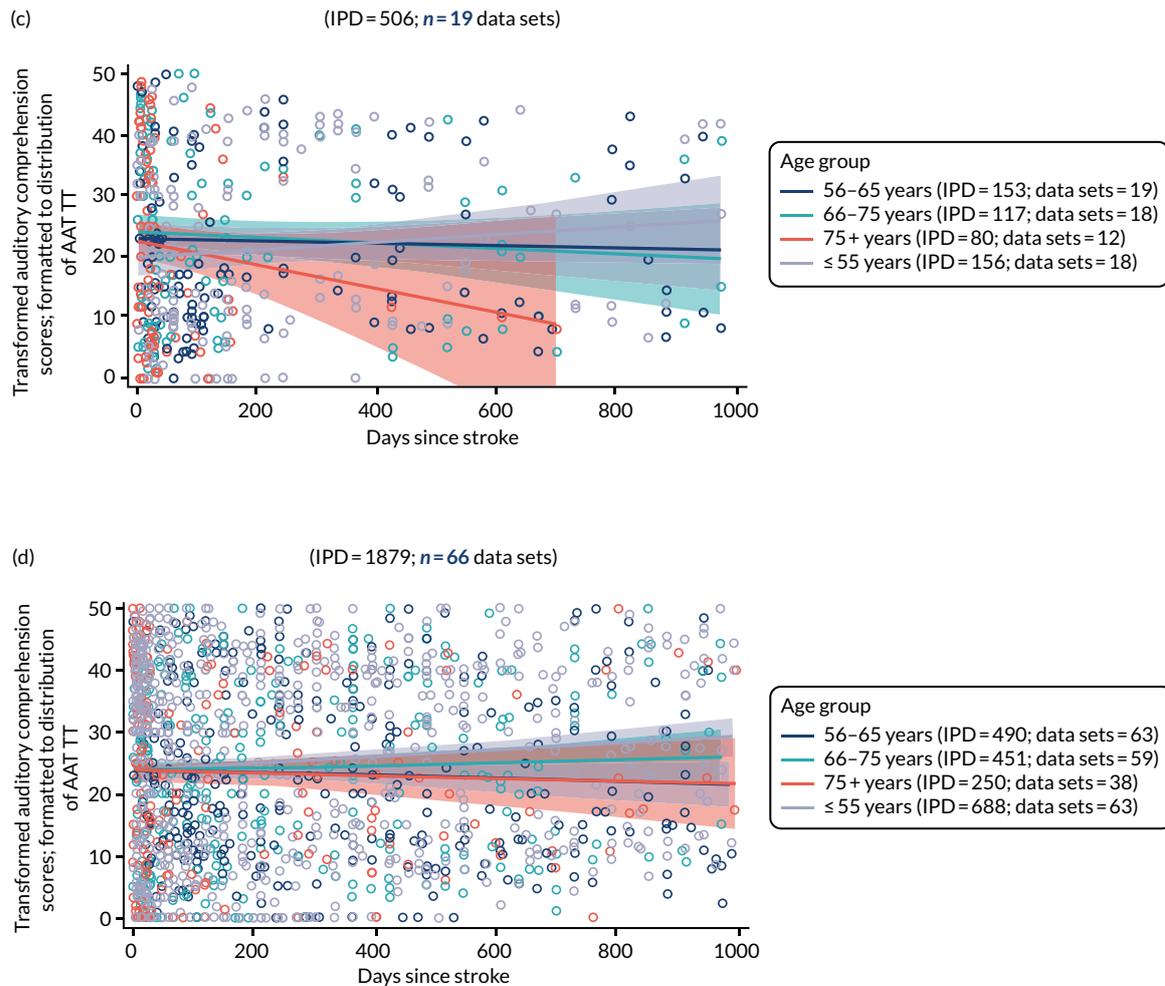


FIGURE 15 Auditory comprehension scores by age for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

### Age and naming at baseline

We examined the distribution of naming scores at baseline by time since stroke and stratified by age in RCTs (748 IPD; 25 RCTs) and in all study designs (2760 IPD; 72 data sets; Figure 16a and 16b).

Participants' naming scores in RCTs were stratified into the following age groups: ≤ 55 years (259 IPD; 25 RCTs), 56–65 years (233 IPD; 24 RCTs), 66–75 years (168 IPD; 24 RCTs) and > 75 years (88 IPD; 16 RCTs) (see Figure 16a). RCT participants aged > 75 years appeared to suggest better naming scores as time since stroke increased at baseline; however, this could be a function of the relatively short time to baseline period for which data on this stratum were available. When examining RCT enrolment within 0–1000 days of stroke, the distribution of naming scores did not appear to differ in those aged > 75 years (see Figure 16c).

We plotted the distribution of participants' naming scores at baseline across all study types and stratified by age (2760 IPD; 72 data sets; see Figure 16b). Data were available for participants aged ≤ 55 years (1005 IPD; 72 data sets), 56–65 years (779 IPD; 71 data sets), 66–75 years (693 IPD; 69 data sets) and > 75 years (283 IPD; 42 data sets). Once again, among participants aged > 75 years, a trend towards better naming scores was apparent when time from stroke to enrolment increased, compared with the younger participant age categories, but this difference was not significant, nor was it evident within 0–1000 days of stroke (see Figure 16b and 16d).

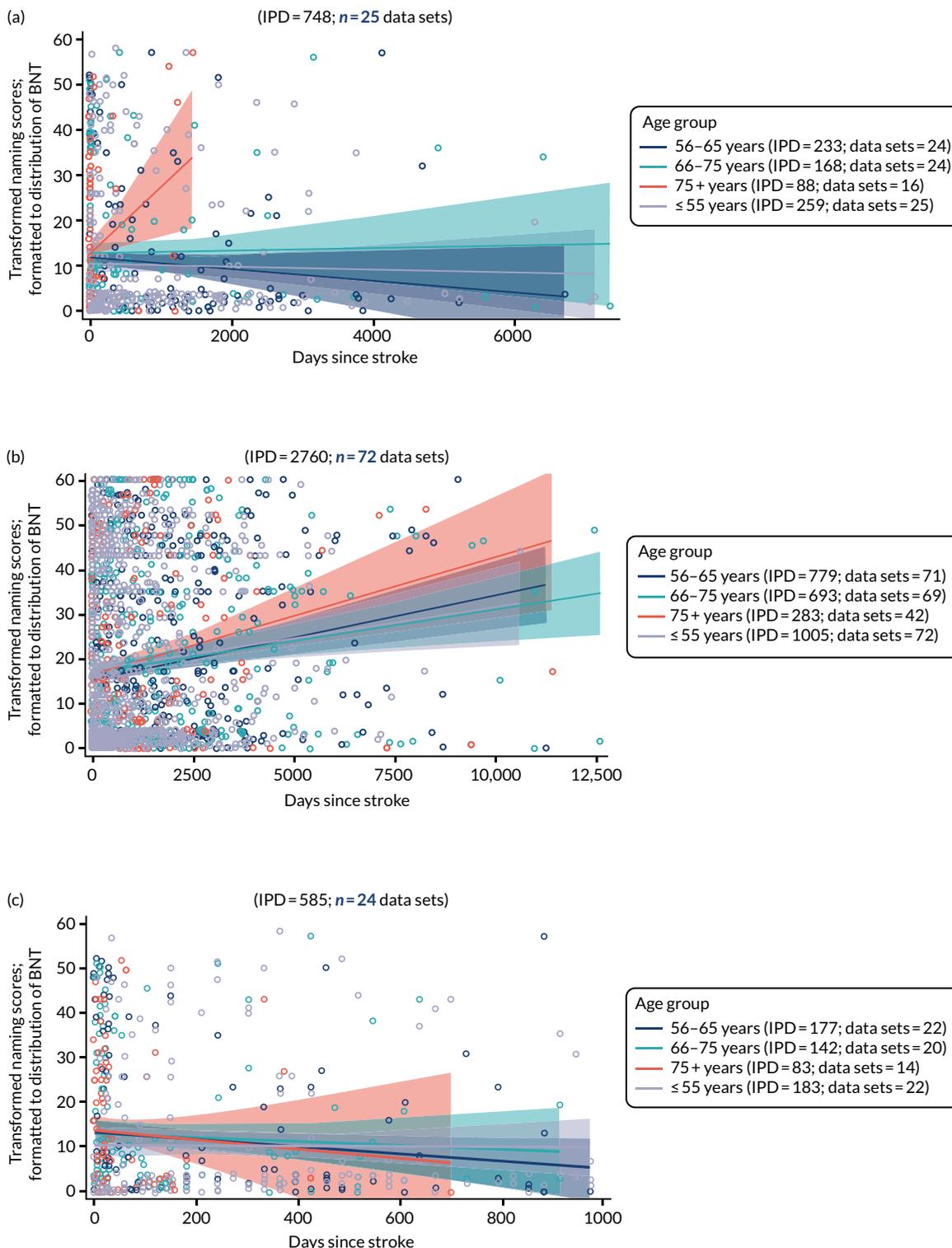


FIGURE 16 Naming scores by age for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

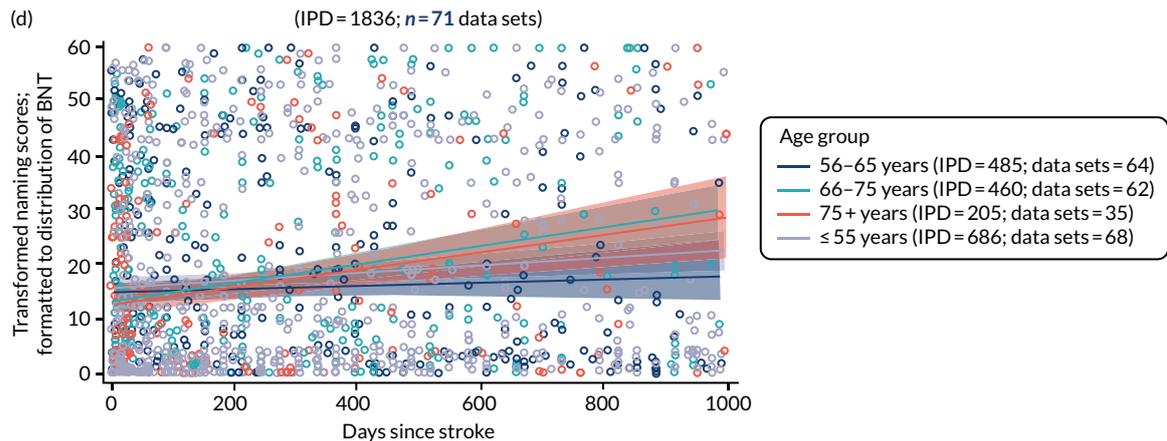


FIGURE 16 Naming scores by age for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

### Age and other spoken language at baseline

We considered the distribution of other spoken-language scores at increasing time from index stroke to study entry, stratified by age, looking first at 163 IPD from two RCTs (see *Report Supplementary Material 4*, figure 1). Data were available for participants aged  $\leq 55$  years (90 IPD; 2 data sets), 56–65 years (58 IPD; 2 data sets) and 66–75 years (15 IPD; 1 data set). There were no IPD for those aged  $> 75$  years.

Other spoken-language scores at baseline remained stable across various times since stroke for the different age groups. There appeared to be no significant differences in the distributions of other spoken-language scores by age group. We found similar distributions in the 344 participants from across seven data sets of all study designs [aged  $\leq 55$  years (191 IPD; 7 data sets), 56–65 years (112 IPD; 7 data sets), 66–75 years (37 IPD; 4 data sets) and  $> 75$  years (4 IPD; 2 data sets)]. Inadequate data on study entry within 0–1000 days of stroke precluded further meaningful analyses of other spoken language (98 IPD; 2 data sets).

### Age and reading comprehension at baseline

We examined the distribution of baseline reading scores at different baseline time points, stratified by age. Data were available from only one RCT and did not meet the prespecified criteria for analysis.

Participants' reading comprehension scores across all study types at baseline (652 IPD; 9 data sets) were distributed across several age groups:  $\leq 55$  years (240 IPD; 8 data sets), 56–65 years (185 IPD; 9 data sets), 66–75 years (160 IPD; 8 data sets) and  $> 75$  years (67 IPD; 6 data sets) (see *Report Supplementary Material 4*, figure 2). Participants aged  $> 75$  years appeared to suggest higher reading scores with greater time since stroke at baseline when compared with participants in the other age groups, but this difference was not significant. We examined whether or not sparse data points at later time points contributed to the slopes of any of the regression lines (see *Report Supplementary Material 4*, figure 2) and found that reading scores at baseline did not significantly differ between different age strata for enrolment within 1000 days of index stroke.

### Age and written language at baseline

We examined the distribution of writing scores among participants across all study types at baseline, stratified by age. There were insufficient data to consider RCT participants' written language scores in isolation: data were available on 47 IPD from three RCTs. For participants across all study types (673 IPD; 11 data sets; *Figure 17a*), data on written language scores were available across the following age groups:  $\leq 55$  years (265 IPD; 11 data sets), 56–65 years (189 IPD; 11 data sets), 66–75 years (156 IPD; 8 data sets) and  $> 75$  years (63 IPD; 5 data sets). There was no evidence of a difference in the distributions of writing scores for different age strata across the whole baseline sample, or when study entry was within 0–1000 days of index stroke.

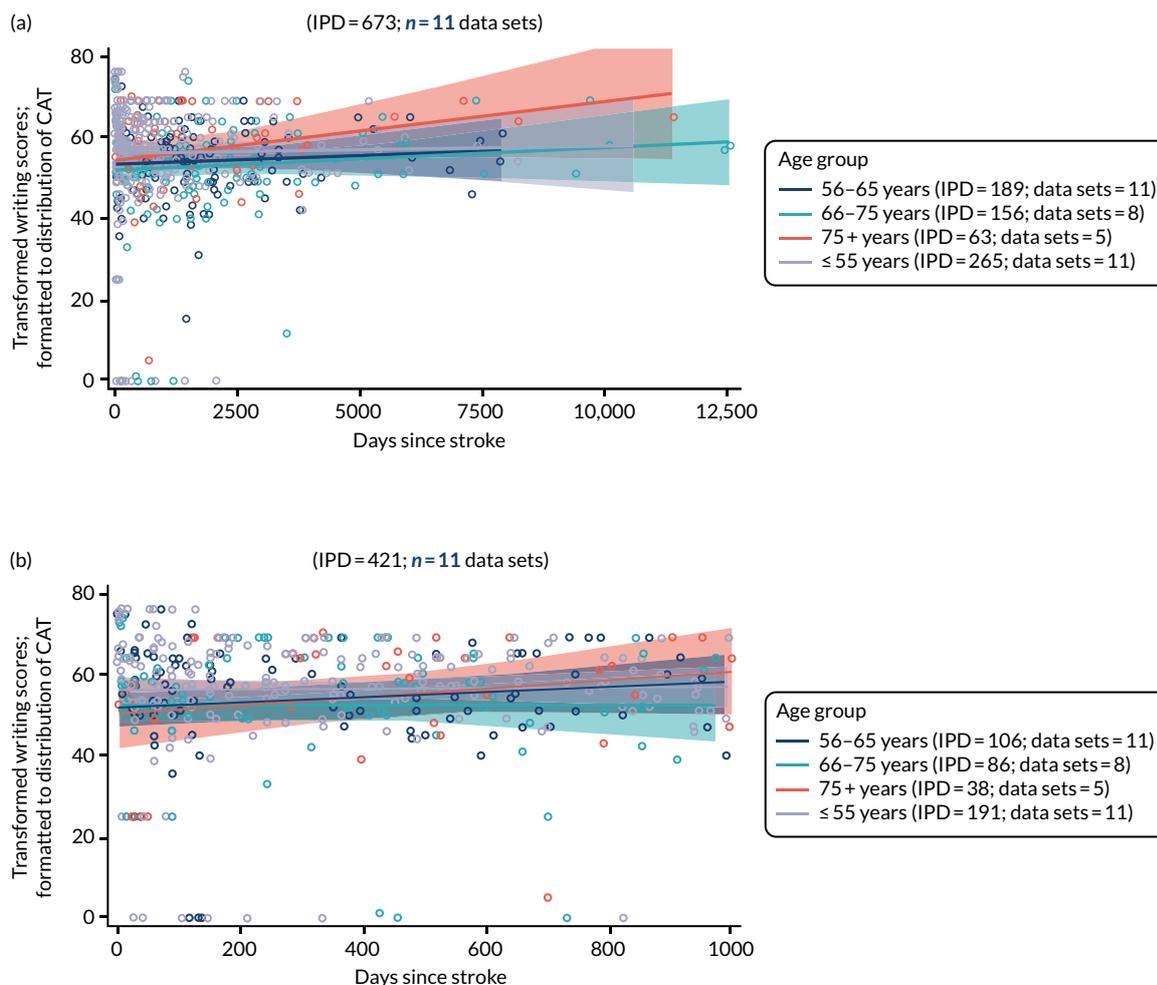


FIGURE 17 Writing scores by age for all participants at baseline. (a) All study types; and (b) for enrolment in all study types within 0–1000 days of stroke.

### Age and observer-rated functional communication (activity) at baseline

We examined the distribution of observer-rated functional communication (activity) in RCTs (998 IPD; 18 RCTs; *Figure 18a*), stratified by four age groups: ≤ 55 years (207 IPD; 18 data sets), 56–65 years (236 IPD; 17 data sets), 66–75 years (283 IPD; 18 data sets) and > 75 years (272 IPD; 15 data sets). Observer-rated activity scores overlapped across each age stratum. This pattern was also seen when examining all study types (1437 IPD; 29 data sets; see *Figure 18b*) and when examining a clinically meaningful enrolment period of 0–1000 days post stroke (see *Figure 18c* and *18d*).

Observer-rated participation scores were based on the same populations, and, similarly, showed no significant differences across each age stratum, regardless of study type and within clinically meaningful enrolment periods.

### Age and self-rated functional communication (activity) at baseline

Data on self-rated functional communication (activity) scores were available on only 11 IPD in one RCT, and therefore did not meet our prerequisites for analysis. For all study types, data were available on 62 IPD from three data sets across all baseline time points, and for 43 IPD from three data sets for which enrolment occurred within 1000 days of index stroke (see *Report Supplementary Material 4*, figure 3). We observed no significant differences in the self-rated functional communication (activity) scores across each age stratum. Data on self-rated functional communication (participation) were derived from the same data set and showed similar results (see *Report Supplementary Material 4*, figure 4).

PREDICTORS OF LANGUAGE RECOVERY

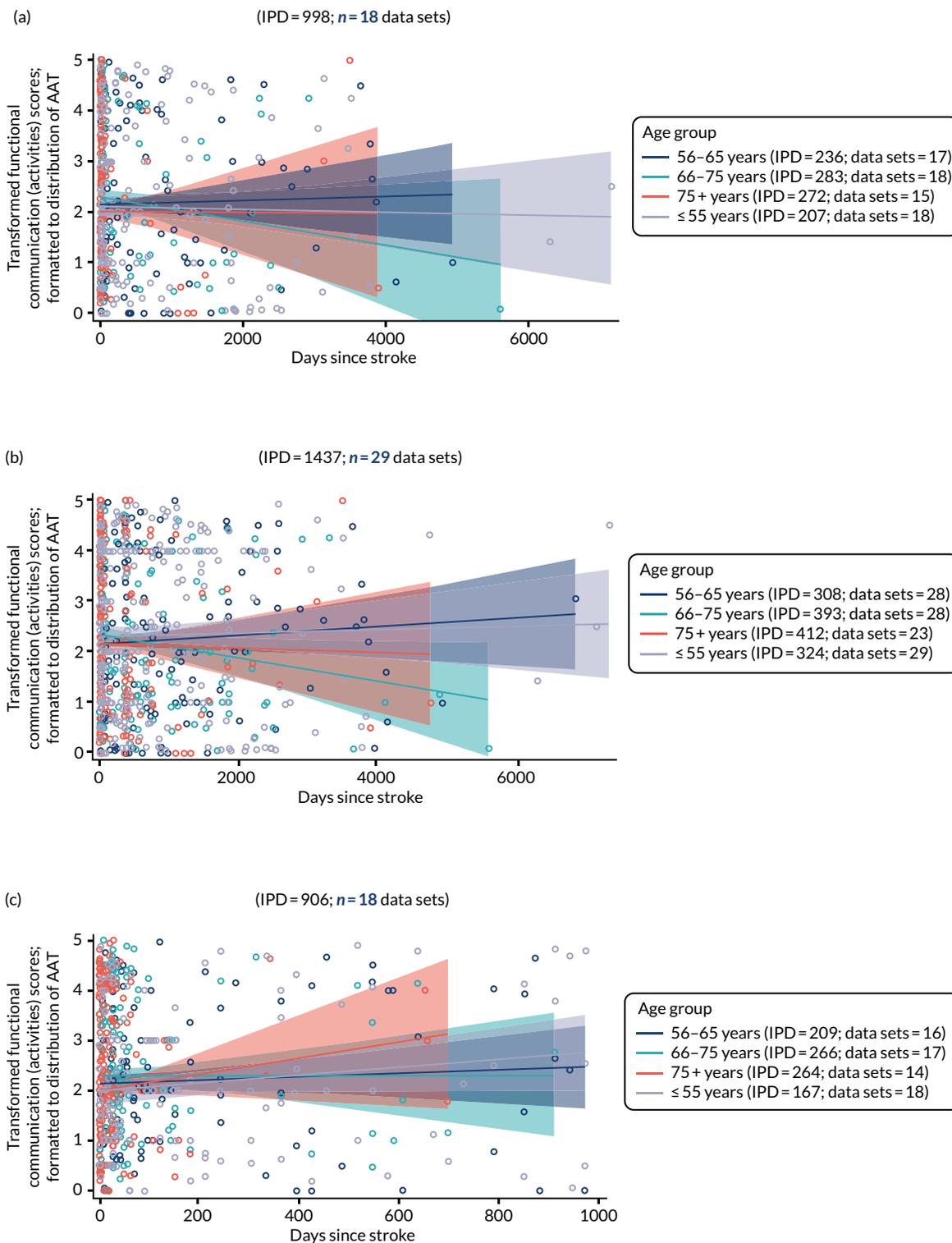


FIGURE 18 Observer-rated functional communication (activity) scores by age for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

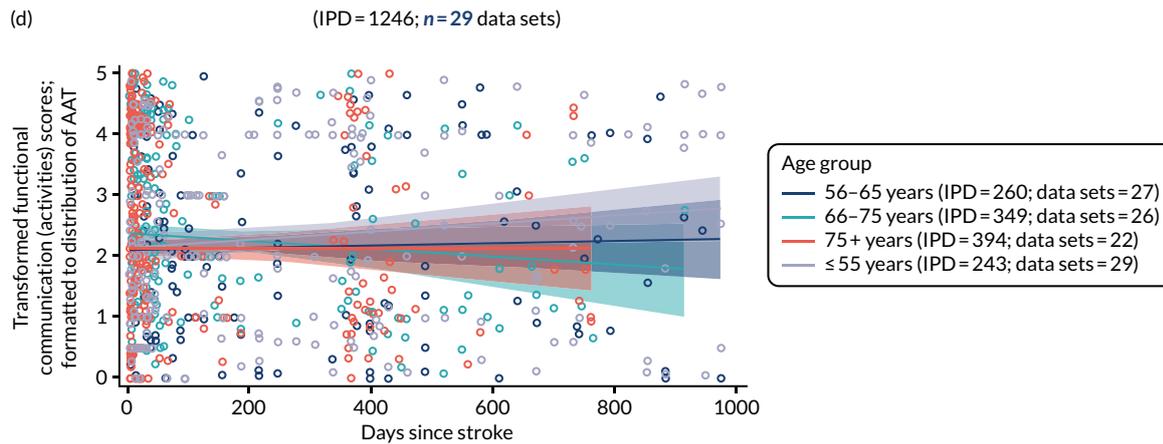


FIGURE 18 Observer-rated functional communication (activity) scores by age for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

## Language performance at baseline, stratified by sex

### Sex and overall language ability at baseline

When data were available, we considered overall language ability at baseline by sex for participants in RCTs (700 IPD; 19 RCTs; *Figure 19*). The confidence bands overlapped, indicating that this difference was not significant. We found similar patterns when we examined IPD across all study designs (2380 IPD; 68 data sets; see *Figure 19b*).

When we examined overall language ability scores within a more clinically relevant time point of 0–1000 days since stroke (599 IPD; 19 data sets; see *Figure 19c*), the data suggested that women appeared to have higher scores at later baseline time points than men, but there was no significant difference in the distributions. The findings were similar when applied to the data gathered at baseline within 1000 days of index stroke from all study designs (1665 IPD; 68 data sets; see *Figure 19d*).

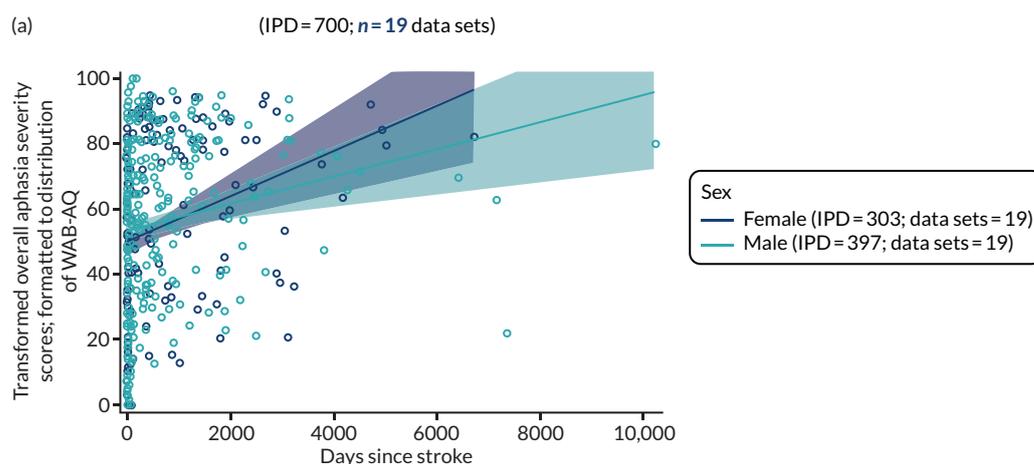


FIGURE 19 Overall language ability scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

PREDICTORS OF LANGUAGE RECOVERY

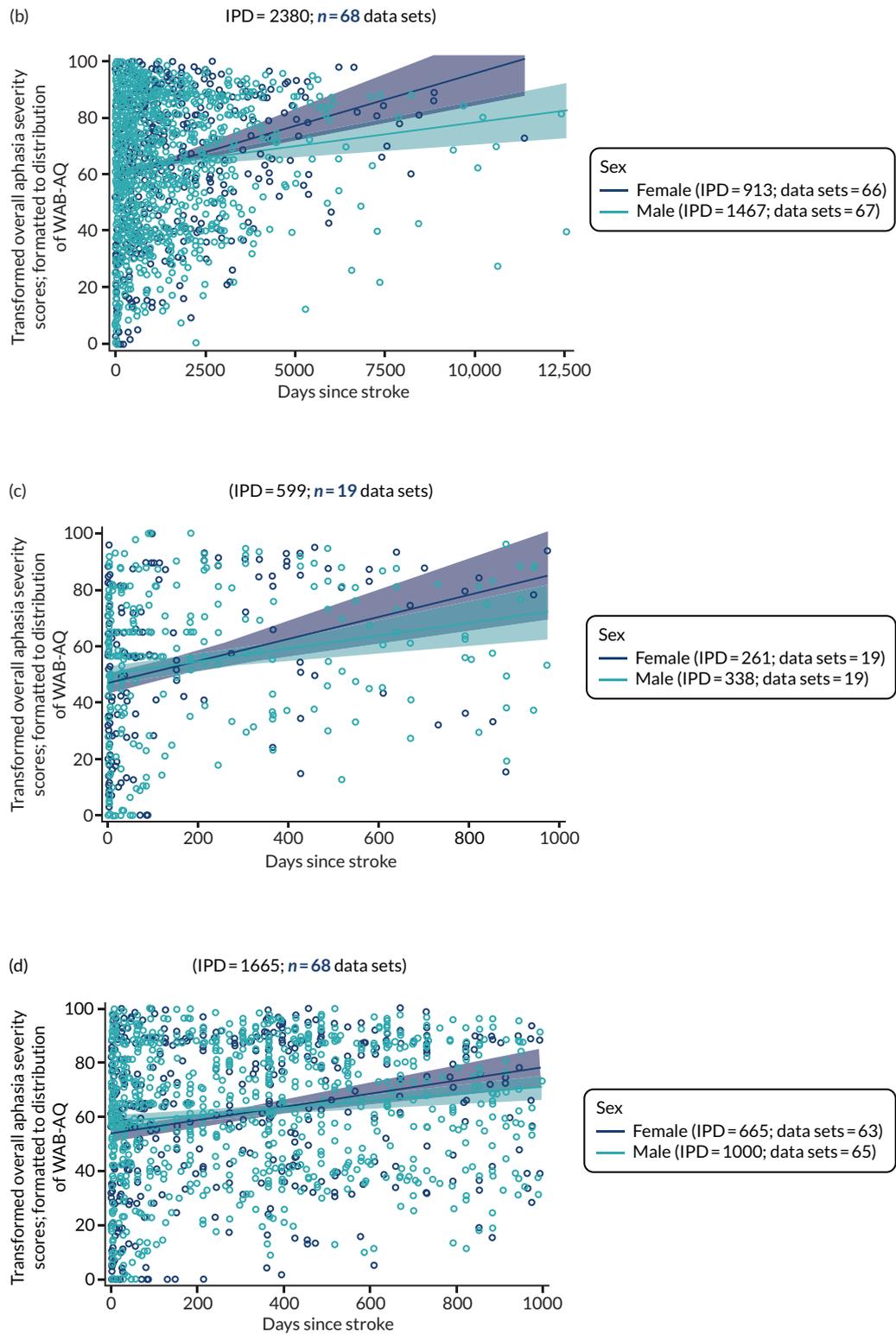


FIGURE 19 Overall language ability scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

### Sex and auditory comprehension at baseline

We stratified the distribution of auditory comprehension scores at baseline time points by sex. Data were available from RCTs (622 IPD; 19 RCTs; *Figure 20a*) and across all study designs (2428 IPD; 60 data sets; see *Figure 20b*). Sex differences were not significant (see *Figure 20*).

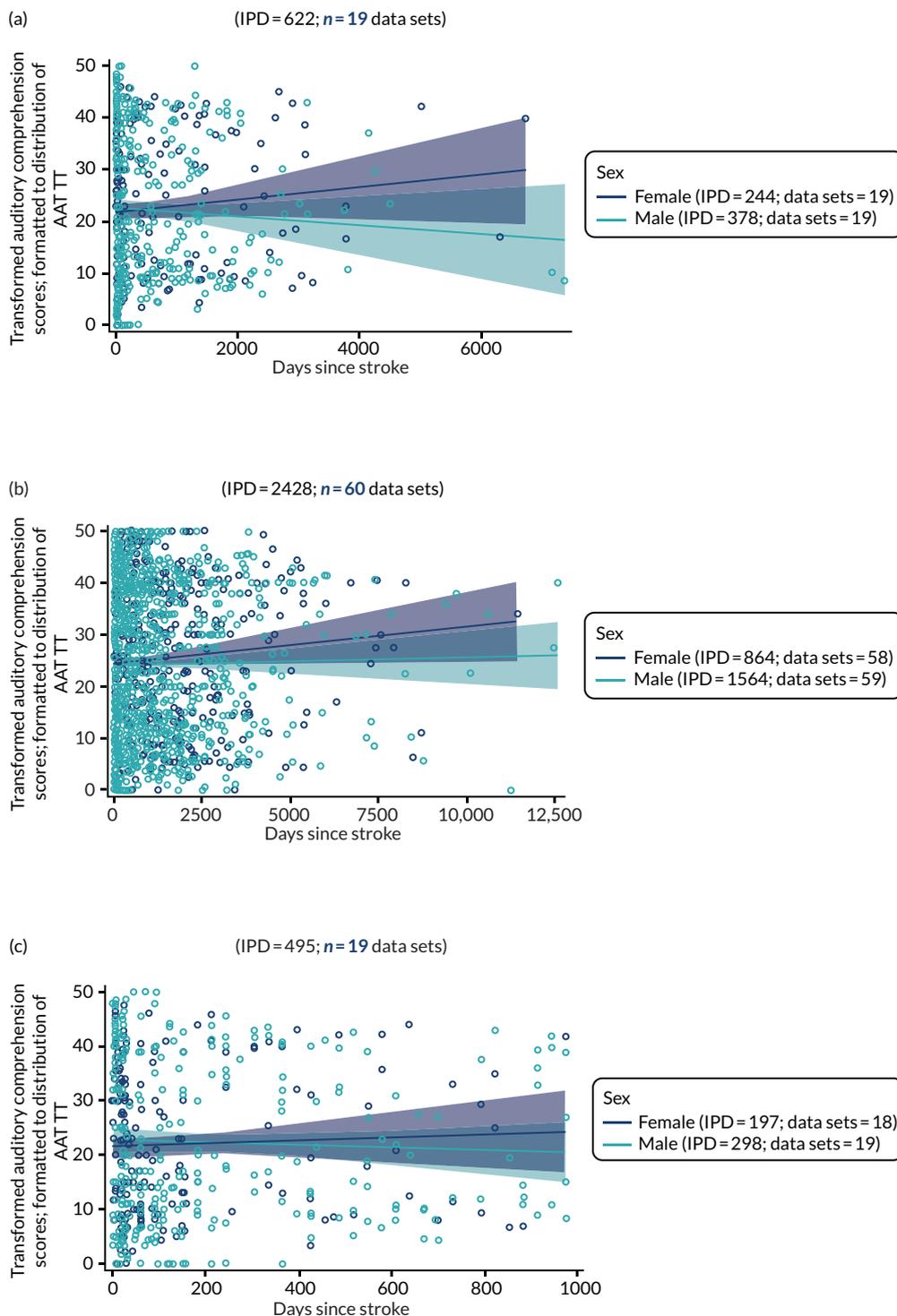


FIGURE 20 Auditory comprehension scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

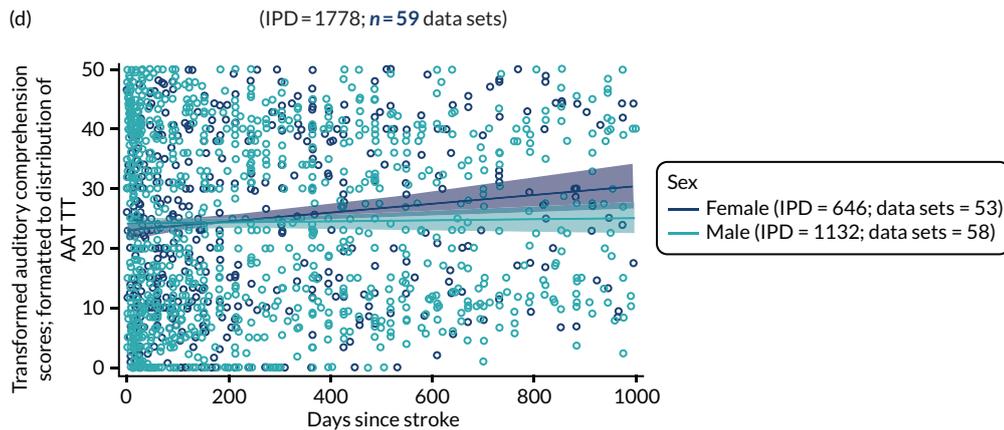


FIGURE 20 Auditory comprehension scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

We then examined whether or not the presence of a smaller number of data points at later baseline time periods influenced the slope of the regression line by plotting scores within a more clinically relevant recruitment period (1778 IPD; 59 data sets; see Figure 20c and d), but we found similar distributions and no evidence of a sex difference.

### Sex and naming at baseline

We examined the available naming data at baseline for RCT data sets (745 IPD; 25 RCTs; Figure 21a) and across all study designs (2629 IPD; 65 data sets; see Figure 21b). With increasing time from stroke to study entry, naming scores declined in the RCT population. Women maintained marginally higher scores than men. However, the confidence limits overlapped, thus indicating that there was no significant sex difference between the distributions of naming scores. Overlapping confidence limits between men and women were also observed across all study designs (see Figure 21b and 21d). When examining these differences in a more clinically relevant enrolment period of 0–1000 days since stroke at baseline, we found a trend towards women having higher naming scores than men, as time to baseline assessment increased in RCTs (583 IPD; 24 RCTs; see Figure 21c) and across all data sets (1766 IPD; 64 data sets; see Figure 21d).

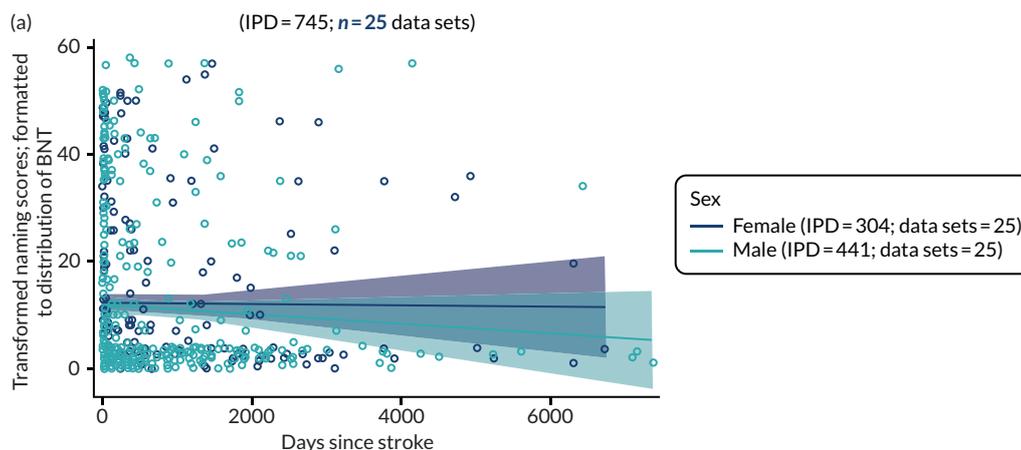


FIGURE 21 Naming scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

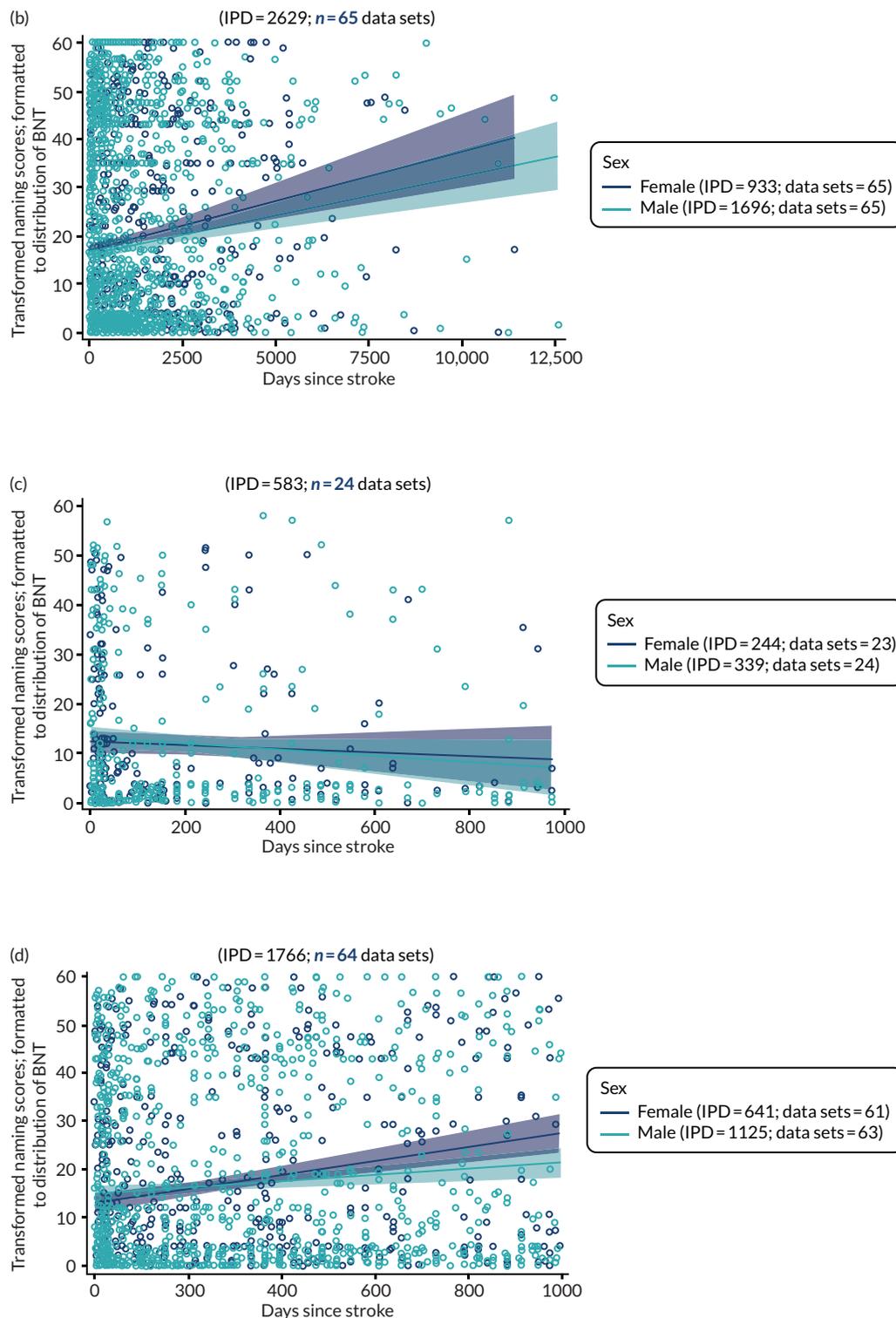


FIGURE 21 Naming scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

### Sex and other spoken language at baseline

We considered the distribution of other spoken-language scores at baseline by time since stroke and stratified by sex for RCT data sets (163 IPD; 2 RCTs; *Figure 22a*) and across all study types (344 IPD; 7 data sets; *Figure 22b*). There did not appear to be any sex differences in the distributions of spoken-language scores at baseline assessment in RCT data sets or across all study designs.

PREDICTORS OF LANGUAGE RECOVERY

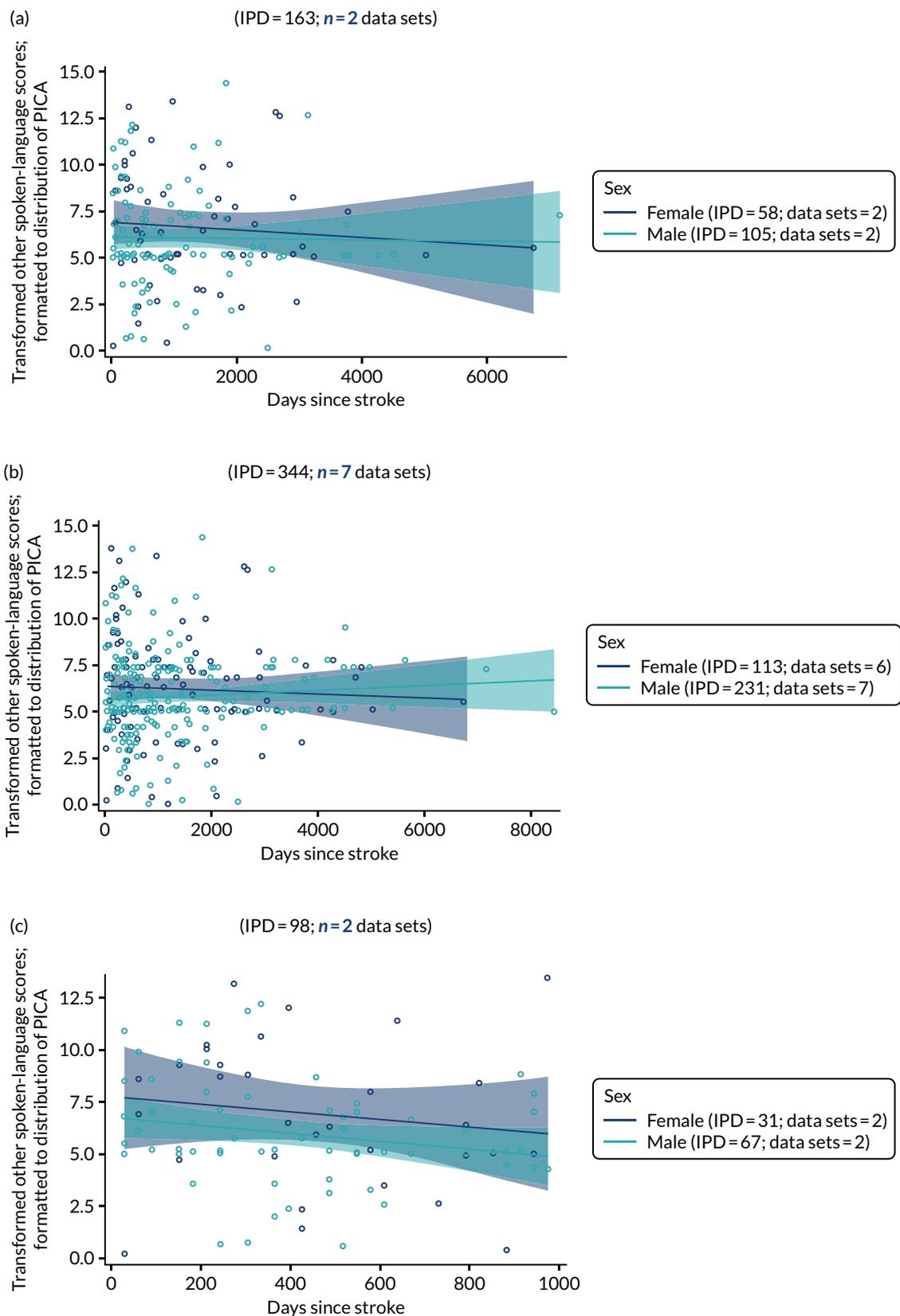


FIGURE 22 Other spoken-language scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

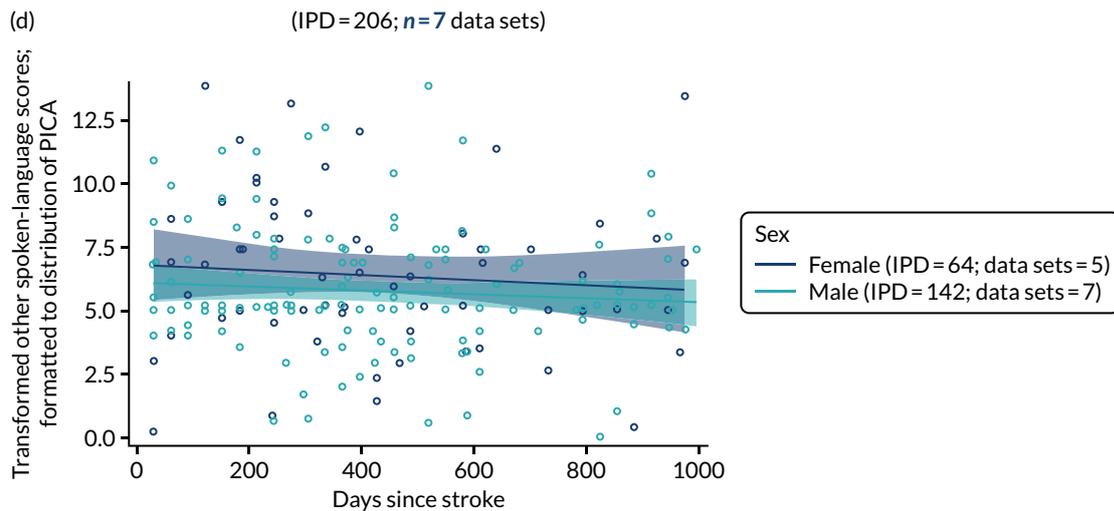


FIGURE 22 Other spoken-language scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

### Sex and reading comprehension at baseline

Data on reading comprehension in the RCT population were available for only 11 IPD in one data set and were therefore not taken forward for further analysis. When data were available, reading comprehension scores at baseline were plotted against time since stroke at baseline and stratified by sex across all study types (652 IPD; 9 data sets; *Figure 23*). Data suggested that women appeared to have better reading scores at baseline time points later after stroke than men at a similar stage since stroke, but this difference was non-significant.

### Sex and writing at baseline

We also examined writing scores at baseline by time since stroke and stratified by sex. In the RCT population (47 IPD; 3 RCTs; *Figure 24a*) and all study types (673 IPD; 11 data sets; see *Figure 24b*), there were no significant differences in writing scores between men and women. Examination of a more clinically relevant time point (of 0–1000 days) also revealed no significant differences between women and men (see *Figure 24c* and *24d*).

### Sex and observer-rated functional communication (activity) at baseline

When examining observer-rated functional communication activity measures (*Figure 25*), men in the RCT population (995 IPD; 18 RCTs) appeared to have better observer-rated activity scores; however, this observation was not apparent when looking at a more clinically relevant enrolment period (see *Figure 25a* and *25c*). In all study types (1434 IPD; 29 data sets; see *Figure 25b*), there was no significant difference in the scores observed between men and women. Observer-rated participation scores were also based on this data set and displayed the same pattern.

### Sex and self-rated functional communication (activity) at baseline

Randomised controlled trial data were available for only 11 IPD from one data set. Therefore, these data were not carried forward to further analyses. Data for self-rated participation scores were also derived from this data set and were also not carried forward to further analyses. Data were available for 62 IPD from three data sets (see *Report Supplementary Material 4*, figure 5). We observed overlaps in activity scores (and participation scores; see *Report Supplementary Material 4*, figure 6) in men and women across all baseline time points, and across all clinically relevant enrolment time points.

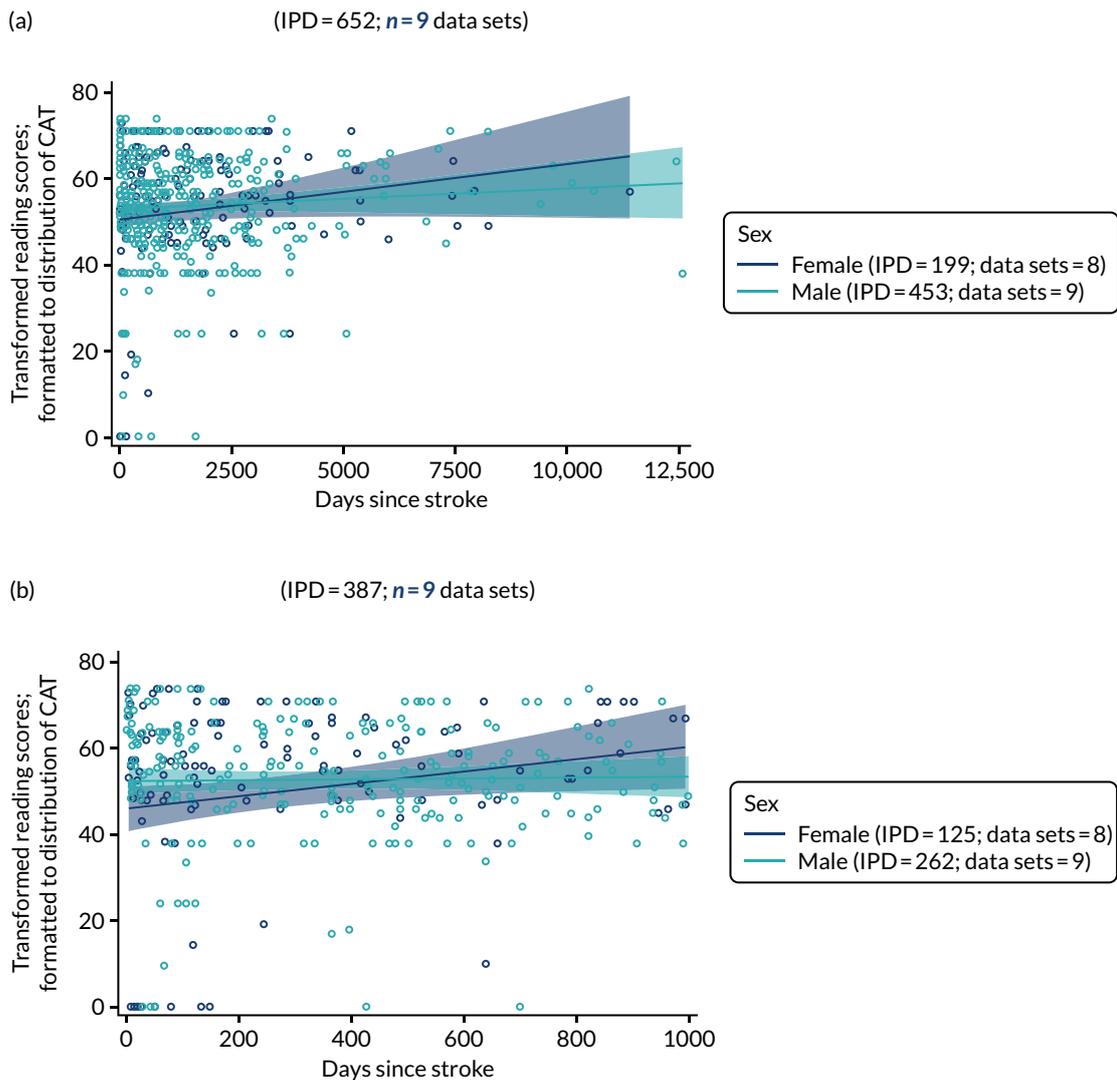


FIGURE 23 Reading comprehension scores by sex for all participants at baseline. (a) All study types; and (b) for enrolment in all study types within 0–1000 days of stroke.

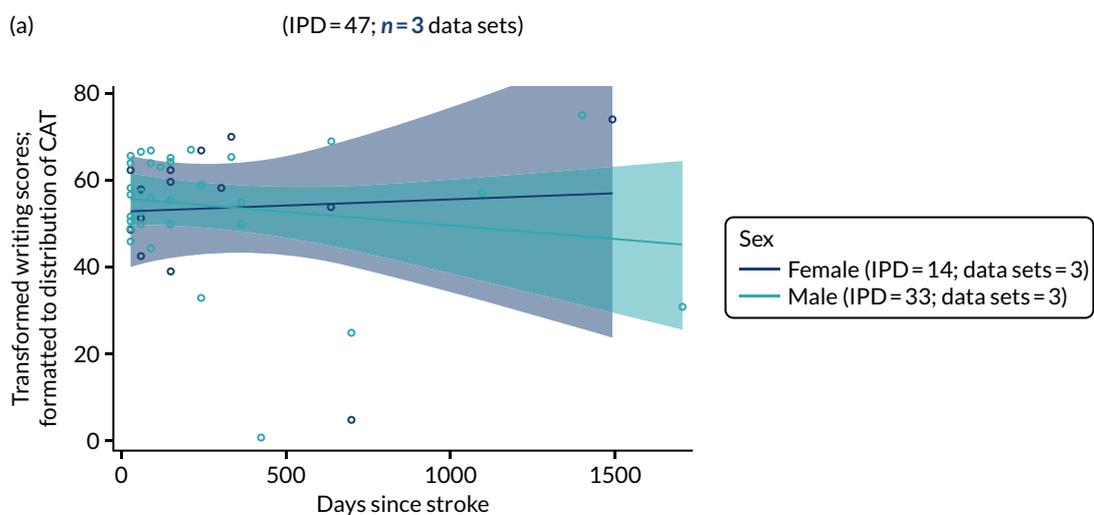


FIGURE 24 Writing scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

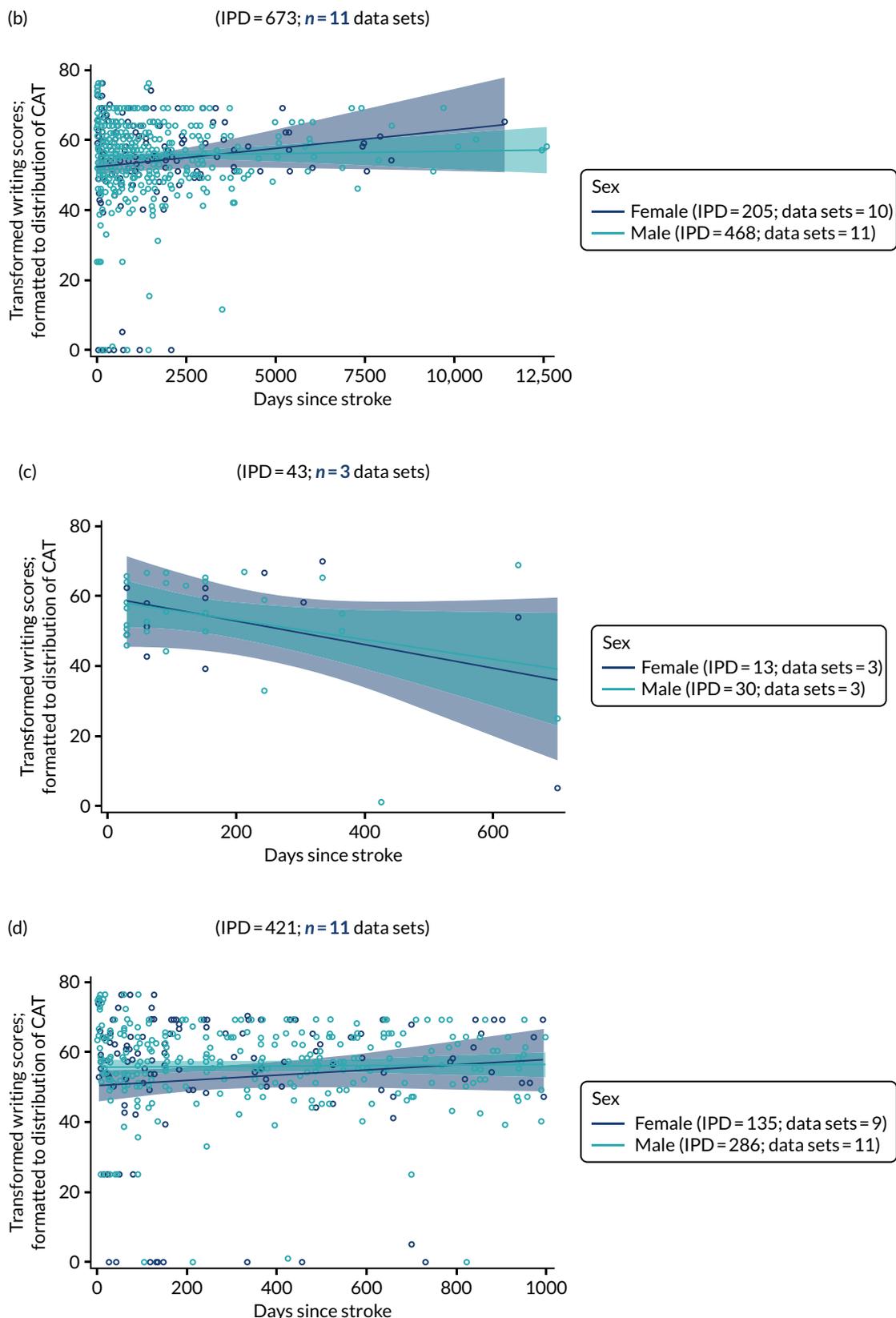


FIGURE 24 Writing scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

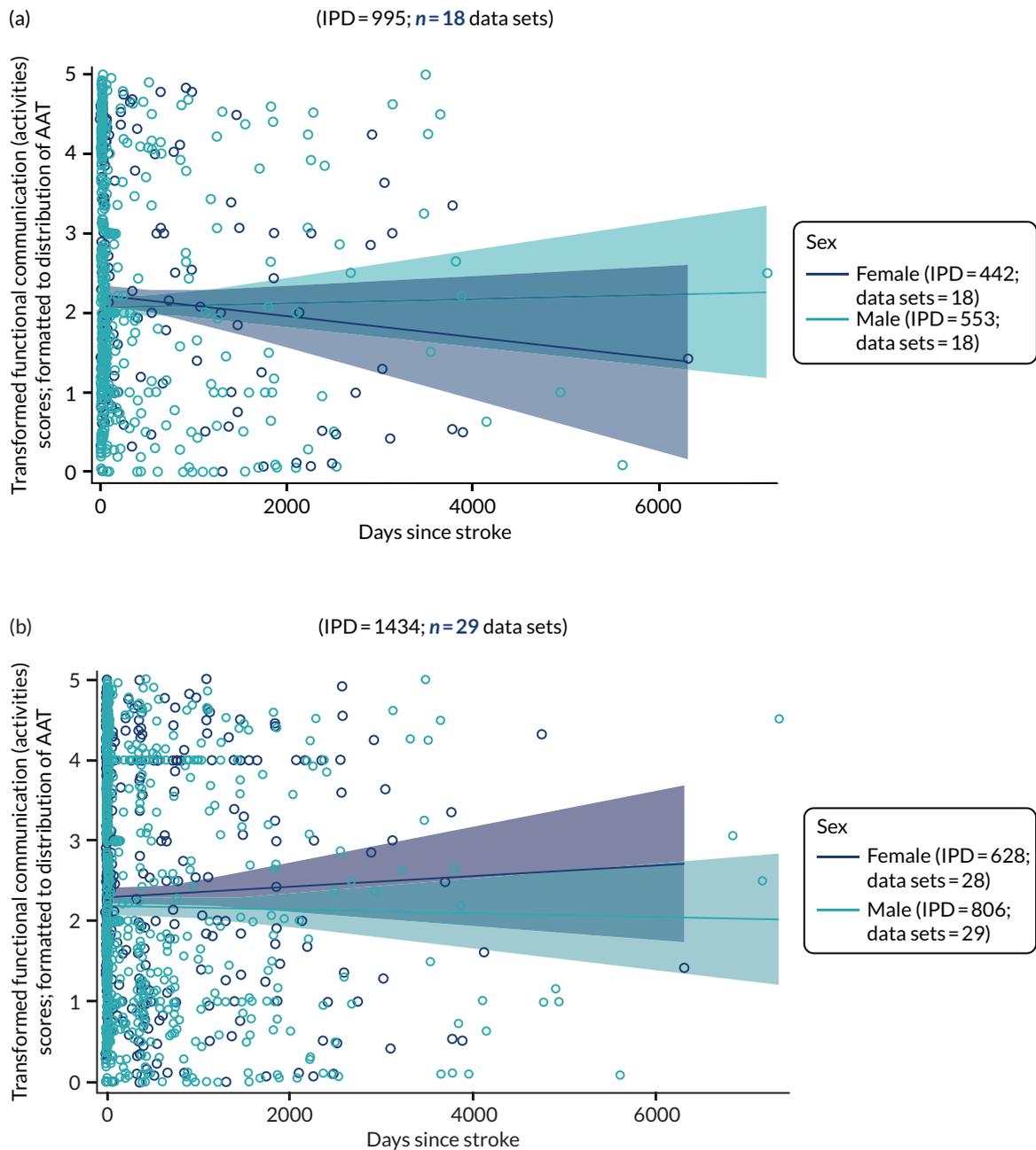


FIGURE 25 Observer-rated functional communication (activity) scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke. (continued)

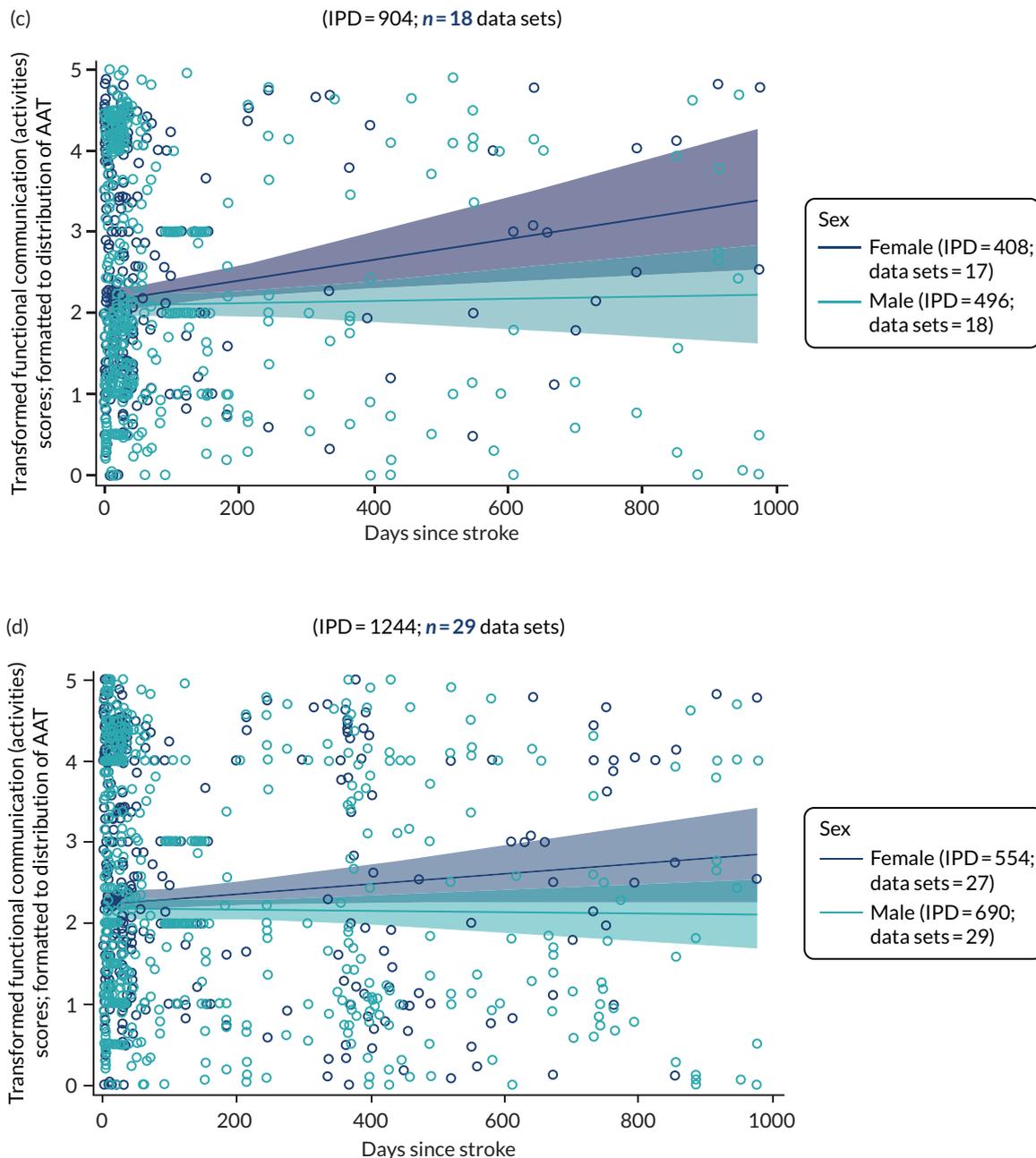


FIGURE 25 Observer-rated functional communication (activity) scores by sex for all participants at baseline. (a) RCTs; (b) all study types; (c) for enrolment in RCTs within 0–1000 days of stroke; and (d) for enrolment in all study types within 0–1000 days of stroke.

## Language performance by living context after stroke

### Living context and overall language ability

When data permitted, we examined the distribution of overall language ability scores at baseline by time since stroke and stratified by living context, in RCTs (158 IPD; 3 RCTs; see *Report Supplementary Material 4*, figure 7) and across all designs (282 IPD; 8 data sets; see *Report Supplementary Material 4*, figure 7). There were insufficient data points to compare overall language ability scores at baseline by living context in RCTs. Using data from all study designs, it appeared that people living in formal care environments trended towards better overall language ability at baseline with greater time since stroke than those who were living alone. However, as the confidence limits overlapped, and there were sparse data points, these differences were not significant.

***Living context and auditory comprehension***

We examined the distribution of auditory comprehension scores at baseline across different time points after stroke and stratified by a participant's living context, in RCT data sets (121 IPD; 3 RCTs; see *Report Supplementary Material 4*, figure 8). There were too few data points with the RCT data to adequately establish a relationship between living context and auditory comprehension scores over time. When we included data from all study designs (143 IPD; 5 data sets), there continued to be inadequate data at common baseline time points to enable comparison of patterns of auditory comprehension scores.

***Living context and naming***

We examined the baseline naming scores at time points since stroke and stratified by living context since stroke among RCT participants (163 IPD; 6 RCTs) and across all study types (176 IPD; 7 data sets; see *Report Supplementary Material 4*, figure 9). There were insufficient data points to adequately examine the differences in participants' living contexts and naming.

***Living context and spoken language, reading comprehension and writing***

We sought data on other spoken-language scores at baseline, by time since stroke and participants' living context after stroke, but identified only 10 IPD (from one data set), preventing further examination. Similarly, we lacked sufficient data to examine reading comprehension (10 IPD; 1 data set) or writing (10 IPD; 1 data set) at baseline.

***Living context and observer-rated functional communication (activity)***

Randomised controlled trial data on observer-rated functional communication (activity) were available for 280 IPD from six data sets, and for 290 IPD from seven data sets for all study types (see *Report Supplementary Material 4*, figure 10). There were inadequate data points at longer times to enrolment to permit reliable analyses or description after stratification by living context. Functional communication (participation) measures were also derived from this data set and showed similar results.

***Living context and self-rated functional communication (activity)***

Only 11 IPD from one RCT were available, which did not meet the prerequisite minimum data set for analysis. There were no further IPD available for self-rated activity or participation by living context across all study types.

Following these exploratory analyses of the data and predictive factors identified in other stroke recovery research,<sup>114-117</sup> we identified age, sex and time since stroke as potential key variables for further examination in relation to recovery and absolute change in scores across each language domain.

***Factors associated with increased proportion of change in each language domain***

We examined the potential factors that were associated with a trend towards a greater absolute percentage change from baseline to first follow-up in each of the language domains using regression and adjusting for common covariates (age, sex and time since stroke), when these data were available.

After excluding participants from the natural history group (who were allocated to no SLT and were enrolled within 15 days of stroke), there were only two RCTs (22 IPD) and three data sets in all study types (34 IPD) comprising participants who received only historical SLT, and for whom data were available at the first follow-up time point following study intervention. For most of this group, participants had been permitted to receive SLT following the study intervention period and had follow-up time points that were inclusive of that usual care intervention. We were thus unable to separate out the effects of only historical SLT from study SLT in these participants. Analyses were therefore based on participants who had access to SLT in all study types to maximise available data.

## Overall language ability

Regression analyses of 418 IPD (11 data sets) on age, sex, time since stroke and overall language ability recovery revealed that increasing the time between stroke onset and study enrolment by 1 month was associated with a 1% decrease in the proportion of change observed for language ability (OR 0.99, 95% CI 0.98 to 1.0;  $p = 0.002$ ) (see Table 7).

TABLE 7 Factors associated with absolute percentage changes in language domain scores from baseline

Domain	Parameter	RCTs			All study types		
		OR	95% CI	p-value	OR	95% CI	p-value
Overall language ability	Age	1.02	1.00 to 1.04	0.02	1.01	1.0 to 1.02	0.08
	Sex (female vs. male)	1.11	0.73 to 1.69	0.62	1.27	0.93 to 1.729	0.14
	Time since stroke <sup>a</sup>	0.99	0.98 to 1.0	0.002	0.99	0.98 to 0.99	< 0.0001
Auditory comprehension	Age	0.99	0.98 to 1.02	0.92	0.98	0.97 to 0.99	0.003
	Sex (female vs. male)	1.40	0.92 to 2.12	0.12	1.32	0.95 to 1.84	0.097
	Time since stroke <sup>a</sup>	0.99	0.99 to 1.00	0.003	0.99	0.99 to 0.99	< 0.0001
Naming	Age	0.99	0.98 to 1.01	0.45	0.99	0.98 to 1.00	0.13
	Sex (female vs. male)	0.95	0.62 to 1.46	0.82	0.98	0.71 to 1.36	0.91
	Time since stroke <sup>a</sup>	0.99	0.98 to 0.99	0.002	0.99	0.99 to 0.99	< 0.0001
Other spoken language	Age	0.97	0.94 to 1.00	0.08	0.97	0.94 to 1.00	0.074
	Sex (female vs. male)	0.99	0.55 to 1.78	0.98	1.04	0.60 to 1.81	0.89
	Time since stroke <sup>a</sup>	0.99	0.98 to 1.0	0.0006	0.99	0.98 to 1.00	0.0012
Reading	Age	-	-	-	0.96	0.94 to 0.99	0.01
	Sex (female vs. male)	-	-	-	0.89	0.40 to 1.95	0.76
	Time since stroke <sup>a</sup>	-	-	-	0.99	0.99 to 1.00	0.004
Writing	Age	1.04	0.99 to 1.10	0.14	0.99	0.97 to 1.02	0.60
	Sex (female vs. male)	0.82	0.25 to 2.72	0.75	0.84	0.45 to 1.58	0.59
	Time since stroke <sup>a</sup>	0.87	0.80 to 0.93	0.0001	1.00	0.99 to 1.00	0.22
Observer-rated functional communication (activity)	Age	1.01	1.00 to 1.03	0.16	1.02	1.00 to 1.03	0.01
	Sex (female vs. male)	1.21	0.84 to 1.75	0.31	1.18	0.84 to 1.64	0.34
	Time since stroke <sup>a</sup>	0.98	0.98 to 0.99	< 0.0001	0.99	0.98 to 0.99	< 0.0001
Observer-rated functional communication (participation)	Age	1.01	1.00 to 1.03	0.16	1.02	1.00 to 1.03	0.01
	Sex (female vs. male)	1.21	0.84 to 1.75	0.31	1.18	0.84 to 1.64	0.34
	Time since stroke <sup>a</sup>	0.98	0.98 to 0.99	< 0.0001	0.99	0.98 to 0.99	< 0.0001
Self-rated functional communication (activity)	Age	-	-	-	0.97	0.93 to 1.02	0.24
	Sex (female vs. male)	-	-	-	2.55	0.65 to 10.04	0.18
	Time since stroke <sup>a</sup>	-	-	-	1.01	0.99 to 1.02	0.37
Self-rated functional communication (participation)	Age	-	-	-	0.97	0.93 to 1.02	0.24
	Sex (female vs. male)	-	-	-	2.55	0.65 to 10.04	0.18
	Time since stroke <sup>a</sup>	-	-	-	1.01	0.99 to 1.02	0.37

a Measured in months.

### Notes

'-' signifies insufficient data. Shading indicated significance.

**Auditory comprehension**

We analysed data on 508 IPD (17 data sets) on the proportion of change in auditory comprehension scores, age, sex and time since stroke. We found that an increase in time since stroke by 1 month was associated with a 1% decrease in the proportion of change in auditory comprehension scores (OR 0.99, 95% CI 0.99 to 1.0;  $p = 0.003$ ; see *Table 7*).

**Naming**

Data were available on 346 IPD (14 data sets) for whom change in naming score, age, sex and time since stroke had been captured. An increase in time since stroke of 1 month was associated with a 1% decrease in the proportion of change in naming scores (see *Table 7*).

**Other spoken language**

Data were available on 155 participants from two data sets for whom change in other spoken-language scores, age, sex and time since stroke were captured. An increase in time since stroke of 1 month was associated with a 1% decrease in the proportion of change since baseline in other spoken-language scores (OR 0.99, 95% CI 0.98 to 1.00;  $p = 0.0006$ ) (see *Table 7*).

**Reading comprehension**

Data were available on 11 IPD from one RCT, and therefore did not meet our prespecified criteria for analysis.

**Writing**

Data were available on 41 IPD (3 RCTs) for whom age, sex, time since stroke and change in writing scores since baseline were captured. Increasing time since stroke was associated with decreased proportion of change in writing score (OR 0.87, 95% CI 0.80 to 0.93;  $p = 0.0001$ ) (see *Table 7*).

**Observer-rated functional communication (activity)**

Data were available on 608 IPD from 16 RCTs for whom observer-rated functional communication (activity) scores, age, sex and time since stroke were captured. An increase by 1 month in time to study entry was associated with a 2% decrease in the proportion of change since baseline in activity (see *Table 7*).

**Observer-rated functional communication (participation)**

Data were available on 608 IPD from 16 RCTs for whom observer-rated functional communication (activity) scores, age, sex and time since stroke were captured. An increase of 1 month in time to study entry was associated with a 2% decrease in the proportion of change since baseline in participation (see *Table 7*).

**Self-rated functional communication**

Data were available from only one RCT, and therefore did not meet our prespecified analysis criteria.

***Factors associated with increased proportion of change using data from all study types*****Overall language ability**

Regression analyses of 749 IPD (19 data sets) on age, sex, time since stroke and overall language ability recovery revealed that an increase of 1 month in the time between stroke onset and study enrolment was associated with a 1% decrease in the proportion of change observed for language ability (OR 0.98, 95% CI 0.98 to 0.99;  $p < 0.0001$ ) (see *Table 7*).

**Auditory comprehension**

We analysed data on 921 IPD (27 data sets) on the proportion of change in auditory comprehension scores, age, sex and time since stroke. This analysis revealed that increasing age (OR 0.98, 95% CI 0.97 to 0.99;  $p = 0.003$ ) was associated with decreased proportion of change and an increase in time since stroke of 1 month was associated with a 1% decrease in the proportion of change in auditory comprehension scores.

### **Naming**

Data were available on 636 IPD (23 data sets) for whom change in naming score, age, sex and time since stroke had been captured. An increase in time since stroke of 1 month was associated with a 1% decrease in the proportion of change in naming scores (see *Table 7*).

### **Other spoken language**

Data were available on 204 participants from five data sets for whom change in other spoken-language scores, age, sex and time since stroke were captured. An increase of 1 month in time since stroke was associated with a 1% decrease in the proportion of change since baseline in other spoken-language scores (OR 0.99, 95% CI 0.98 to 1.00;  $p = 0.0012$ ) (see *Table 7*).

### **Reading comprehension**

Data were available on 145 IPD (3 data sets) for whom change in reading scores, age, sex and time since stroke were captured. An increase of 1 year in age was associated with a decreased proportion of change in reading comprehension (OR 0.96, 95% CI 0.94 to 0.99;  $p = 0.01$ ) (see *Table 7*). Increasing the time since stroke to study inclusion by 1 month was associated with a 1% decrease in the proportion of change in reading scores.

### **Writing**

Data were available on 208 IPD (7 data sets) for whom age, sex, time since stroke and change in writing scores since baseline were captured. Age, sex and time since stroke were each not associated with proportion of change in writing score (see *Table 7*).

### **Observer-rated functional communication (activity)**

Data were available on 802 IPD from 22 data sets for whom observer-rated functional communication (activity) scores, age, sex and time since stroke were captured. An increase of 1 month in time to study entry was associated with a 1% decrease in the proportion of change since baseline in activity (see *Table 7*).

### **Observer-rated functional communication (participation)**

Data were available on 755 IPD from 21 data sets for whom observer-rated functional communication (participation) scores, age, sex and time since stroke were captured. An increase of 1 month in time to study entry was associated with a 1% decrease in the proportion of change since baseline in activity (see *Table 7*).

### **Self-rated functional communication (activity)**

Data were available on 43 IPD from two data sets for whom self-rated functional communication (activity) scores were available. Age, sex and time since stroke were not significantly associated with recovery, although the sample was very small.

### **Self-rated functional communication (participation)**

Data were available on 43 IPD from two data sets for whom self-rated functional communication (participation) scores were available. Age, sex and time since stroke were not significantly associated with recovery, although the sample was very small.

### ***Predictors of recovery following aphasia after stroke***

We sought to examine the predictors of aphasia recovery across seven language domains in relation to participant demographics and stroke profile. Generalised linear models were used to estimate the impact of the initial severity of language impairment on subsequent recovery outcomes (defined as the absolute changes in raw scores since baseline), and this was repeated for each language domain (overall language ability, auditory comprehension, naming, other spoken language, reading comprehension, writing and functional communication).

In these analyses, we quantified the association between aphasia and eight variables (baseline score, sex, hemisphere of stroke, type, handedness, language used, age and time since stroke) using univariable and multivariable analyses. We considered language measures at baseline and first post-intervention period follow-up.

There were insufficient data on bilingualism (12 IPD available). Data on ethnicity (1475 IPD available) were also limited, but were further minimised as the variable was distributed across seven possible categories. Socioeconomic status was reported in several formats and no single composite score could be derived to describe socioeconomic status across data sets. Educational history was reported for 3125 IPD, but the variable was recorded in multiple formats, including ‘years spent in education’, ‘highest qualification’ and ‘age on leaving full-time education, making synthesis of these variables uncertain. Alternatively, analysis of years of education alone resulted in an insufficient data set. Consequently, we did not consider monolingualism/multilingualism, ethnicity, socioeconomic status or educational history in our analysis. Similarly, when a variable at each level was available only in an isolated data set, the effect of that variable on the outcome could not be distinguished from the study effect. In such cases, it was not possible to calculate estimates of the effect for non-English languages.

We first retrieved the key demographic data and identified the availability of overlapping IPD with interventions data, before excluding duplicate records, IPD that had no baseline or no follow-up data points, and non-RCT data (see *Table 5*). We then looked at the availability of IPD on age, sex, handedness, language used, stroke type, hemisphere, time since stroke and aphasia baseline score which would inform our planned analyses (see *Appendix 8, Table 15*). As prespecified, we removed variables with missing data > 20% and adjusted for initial aphasia severity. Sex, time since stroke and age are key predictive factors in recovery from stroke;<sup>114–117</sup> although they were not always significant in this model, we included them in the analysis of population characteristics to adjust for differences between studies and changes in magnitude of effect and to inform later stages of the analyses (*Table 8*).

**TABLE 8** Predictors of language recovery following aphasia after stroke: data sets, IPD and multivariable estimates of means (95% CIs) from RCTs and all data sets

Parameter	RCTs				All data sets			
	Data sets (n)	IPD (n)	Estimate of means	95% CI	Data sets (n)	IPD (n)	Estimate of means	95% CI
<b>Overall language ability, WAB-AQ</b>								
<i>Sex</i>								
Female	11	206	14.25	9.01 to 19.50	16	250	14.15	9.66 to 18.65
Male	11	276	12.30	7.16 to 17.44	17	378	12.17	7.89 to 16.46
<i>Age (years)</i>								
≤ 55	11	136	15.43	9.95 to 20.91	17	192	16.51	10.03 to 22.99
56–65	11	141	12.36	6.90 to 17.82	16	178	12.88	6.38 to 19.38
66–75	10	96	11.49	5.73 to 17.25	14	123	13.22	6.69 to 19.75
> 75	7	109	13.81	7.82 to 19.81	9	135	13.83	6.94 to 20.73
<i>Time since stroke</i>								
0–1 month	8	260	19.14	13.89 to 24.39	9	335	20.99	13.78 to 28.20
> 1–3 months	6	64	16.17	10.20 to 22.13	8	71	16.44	9.02 to 23.86
> 3–6 months	3	16	9.60	0.07 to 19.14	5	19	9.58	–0.07 to 19.22
> 6 months	4	142	8.19	–0.12 to 16.50	8	203	9.44	2.81 to 16.07
			Random (no)		6	146	14.17	7.36 to 20.99
			Random (yes)		11	482	12.37	7.70 to 17.04

TABLE 8 Predictors of language recovery following aphasia after stroke: data sets, IPD and multivariable estimates of means (95% CIs) from RCTs and all data sets (continued)

Parameter	RCTs				All data sets			
	Data sets (n)	IPD (n)	Estimate of means	95% CI	Data sets (n)	IPD (n)	Estimate of means	95% CI
<b>Auditory comprehension on TT-AAT</b>								
Sex								
Female	16	211	3.82	0.98 to 6.66	22	239	4.92	2.15 to 7.70
Male	16	329	3.10	0.35 to 5.85	21	402	4.35	1.65 to 7.04
Age (years)								
≤ 55	16	178	6.05	3.16 to 8.94	22	232	7.05	4.32 to 9.77
56–65	16	182	2.83	–0.04 to 5.71	22	212	4.31	1.52 to 7.09
66–75	15	116	3.50	0.46 to 6.53	19	131	4.61	1.65 to 7.58
> 75	12	64	1.46	–1.90 to 4.82	14	66	2.57	–0.74 to 5.88
Time since stroke								
0–1 month	6	139	5.25	1.69 to 8.82	6	139	6.33	2.57 to 10.08
> 1–3 months	9	97	4.27	1.07 to 7.47	10	106	5.16	1.99 to 8.34
> 3–6 months	6	61	2.88	–1.81 to 7.56	8	65	4.32	0.04 to 8.60
> 6 months	9	243	1.44	–1.85 to 4.72	15	331	2.73	0.12 to 5.34
			Random (no)		5	101	6.11	1.65 to 10.57
			Random (yes)		16	540	3.16	0.67 to 5.65
<b>Naming on BNT</b>								
Sex								
Female	13	165	6.92	2.47 to 11.36	21	219	7.54	3.84 to 11.23
Male	13	220	6.70	2.33 to 11.07	21	333	7.73	4.10 to 11.36
Age (years)								
≤ 55	13	103	9.31	4.71 to 13.90	21	181	9.72	6.00 to 13.44
56–65	13	124	7.34	2.79 to 11.90	21	169	8.08	4.30 to 11.87
66–75	12	97	6.16	1.48 to 10.84	18	134	7.35	3.48 to 11.22
> 75	11	61	4.42	–0.56 to 9.40	15	68	5.38	1.11 to 9.66
Time since stroke								
0–1 month	5	129	11.12	5.71 to 16.54	6	138	11.35	6.62 to 16.09
> 1–3 months	8	93	7.74	2.89 to 12.59	10	116	8.70	4.56 to 12.84
> 3–6 months	6	70	4.26	–1.58 to 10.10	9	92	5.70	1.17 to 10.23
> 6 months	7	93	4.11	–1.08 to 9.29	15	206	4.78	1.08 to 8.48
			Random (no)		8	167	8.56	2.88 to 14.24
			Random (yes)		13	385	6.71	2.57 to 10.85
<b>Other spoken language on the PICA</b>								
Sex								
Female	3	67	–	–	5	73	1.02	0.33 to 1.73
Male	3	115	–	–	6	158	0.93	0.32 to 1.57

continued

TABLE 8 Predictors of language recovery following aphasia after stroke: data sets, IPD and multivariable estimates of means (95% CIs) from RCTs and all data sets (continued)

Parameter	RCTs				All data sets			
	Data sets (n)	IPD (n)	Estimate of means	95% CI	Data sets (n)	IPD (n)	Estimate of means	95% CI
<b>Age (years)</b>								
≤ 55	3	93	-	-	6	119	1.18	0.54 to 1.86
56-65	3	64	-	-	6	82	0.71	0.07 to 1.39
66-75	2	25	-	-	4	30	1.03	0.24 to 1.87
> 75	0	0	-	-	0	0	-	-
<b>Time since stroke</b>								
0-1 month	1	12	-	-	1	12	1.29	0.14 to 2.55
> 1-3 months	2	23	-	-	3	31	1.94	1.13 to 2.78
> 3-6 months	1	6	-	-	2	8	0.27	-0.90 to 1.56
> 6 months	2	141	-	-	5	180	0.46	-0.12 to 1.07
<b>Reading on the CAT</b>								
<b>Sex</b>								
Female	1	0	-	-	3	30	0.92	-1.27 to 3.47
Male	1	0	-	-	4	58	0.87	-1.02 to 3.03
<b>Age (years)</b>								
≤ 55	1	2	-	-	4	32	5.54	2.65 to 8.91
56-65	1	2	-	-	4	25	-0.87	-3.03 to 1.68
66-75	1	5	-	-	3	24	1.53	-0.87 to 4.34
> 75	1	2	-	-	3	7	-1.68	-5.00 to 2.73
<b>Time since stroke</b>								
0-1 month	0	0	-	-	1	9	-0.38	-3.71 to 3.93
> 1-3 months	0	0	-	-	1	15	3.97	0.55 to 8.14
> 3-6 months	0	0	-	-	1	18	0.42	-2.22 to 3.61
> 6 months	1	11	-	-	4	46	-0.06	-1.92 to 2.06
<b>Writing on the CAT</b>								
<b>Sex</b>								
Female	3	14	2.87	-2.35 to 8.08	3	14	RCT data only	RCT data only
Male	3	33	3.72	-1.39 to 8.82	3	33	RCT data only	RCT data only
<b>Age (years)</b>								
≤ 55	3	24	2.92	-0.97 to 6.82	3	24	RCT data only	RCT data only
56-65	3	15	0.21	-4.86 to 5.29	3	15	RCT data only	RCT data only
66-75	2	6	4.43	-3.55 to 12.40	2	6	RCT data only	RCT data only
> 75	1	2	5.60	-7.47 to 18.66	1	2	RCT data only	RCT data only
<b>Time since stroke</b>								
0-1 month	0	0	-	-	0	0	-	-
> 1-3 months	2	21	7.84	2.26 to 13.43	2	21	RCT data only	RCT data only
> 3-6 months	2	8	3.06	-4.33 to 10.46	2	8	RCT data only	RCT data only
> 6 months	3	18	-1.04	-5.55 to 3.48	3	18	RCT data only	RCT data only

TABLE 8 Predictors of language recovery following aphasia after stroke: data sets, IPD and multivariable estimates of means (95% CIs) from RCTs and all data sets (continued)

Parameter	RCTs				All data sets			
	Data sets (n)	IPD (n)	Estimate of means	95% CI	Data sets (n)	IPD (n)	Estimate of means	95% CI
<b>Functional communication (observer-rated), AAT-SSC</b>								
Sex								
Female	14	237	0.76	0.48 to 1.03	18	275	0.69	0.40 to 0.98
Male	14	296	0.57	0.30 to 0.84	19	372	0.54	0.26 to 0.83
Age (years)								
≤ 55	14	147	0.75	0.46 to 1.04	19	181	0.69	0.39 to 0.99
56–65	13	145	0.70	0.41 to 1.00	18	170	0.66	0.36 to 0.96
66–75	14	122	0.55	0.25 to 0.85	18	148	0.52	0.21 to 0.82
> 75	12	119	0.65	0.34 to 0.96	15	148	0.61	0.30 to 0.92
Time since stroke								
0–1 month	6	232	1.05	0.70 to 1.40	7	277	0.97	0.61 to 1.34
> 1–3 months	5	68	0.87	0.51 to 1.23	6	70	0.83	0.46 to 1.21
> 3–6 months	4	63	0.40	–0.06 to 0.87	5	63	0.37	–0.10 to 0.83
> 6 months	7	170	0.33	0.00 to 0.66	11	237	0.30	0.01 to 0.60
			Random (no)		5	115	0.57	0.11 to 1.03
			Random (yes)		14	532	0.67	0.41 to 0.94
<b>Functional communication (self-rated), Assessment for Living with Aphasia</b>								
Sex								
Female	1	4	–	–	2	9	–	–
Male	1	7	–	–	2	34	–	–
Age (years)								
≤ 55	1	2	–	–	2	16	–	–
56–65	1	2	–	–	2	9	–	–
66–75	1	5	–	–	2	15	–	–
> 75	1	2	–	–	2	3	–	–
Time since stroke								
0–1 month	0	0	–	–	0	0	–	–
> 1–3 months	0	0	–	–	0	0	–	–
> 3–6 months	0	0	–	–	0	0	–	–
> 6 months	1	11	–	–	2	43	–	–
<b>Notes</b>								
‘–’ indicates insufficient data.								
Shading indicates significant change from baseline.								
Reproduced with permission from Ali <i>et al.</i> <sup>118</sup> This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <a href="https://creativecommons.org/licenses/by/4.0/">https://creativecommons.org/licenses/by/4.0/</a> . The table includes minor additions and formatting changes to the original table.								

### Overall language ability

Eleven RCTs (518 IPD) had data on overall language ability at study baseline, but only 482 IPD had both baseline and follow-up data of an SLT intervention and were eligible for analysis. Missing data were observed for the following variables: education (56%), handedness (44%), ethnicity (95%) and hemisphere of stroke (30%).

### Demographic analysis

The outcome was absolute change in the raw score from baseline to the first follow-up after the study intervention period. A positive change indicated an improvement in overall language abilities. At univariable level, we observed statistically significant associations between baseline measures of language ability and positive change at follow-up ( $p < 0.0001$ ; see *Appendix 8, Table 15*). Length of time since the onset of aphasia (grouped) was also a significant predictor of improvement ( $p = 0.017$ ). As initial language ability scores at baseline were strongly associated with an increase in overall language abilities at follow-up, we examined an adjusted association between time since stroke and baseline language ability in a bivariable model (see *Appendix 8, Table 15*).

After adjusting for the effect of baseline language ability score, time since stroke was no longer associated with overall language ability scores at follow-up, whereas the language spoken by participants became significant ( $p = 0.021$ ); however, as highlighted in *Predictors of recovery following aphasia after stroke*, this finding should be treated with caution as there were no within-data set comparisons of languages spoken and so it was not possible to distinguish a language effect from a data set effect.

The multivariable analysis revealed a similar finding, with language ability scores at baseline continuing to have a significant, positive association with language ability scores at follow-up. When handedness was included in this multivariable analysis, language ability at baseline, sex and language used were all significantly positively associated with recovery (see *Appendix 8, Table 15*).

We observed slightly better improvement on measures of overall language ability among women than men [female estimate mean 14.3 points (95% CI 9.01 to 19.5 points) vs. male estimate mean 12.3 points (95% CI 7.2 to 17.4 points); see *Table 8*]; however, this difference was not significant ( $p = 0.1870$ ) (see *Appendix 8, Table 15*). We also observed a non-significant trend towards improvements among younger participants and those in the early stages after stroke (see *Appendix 8, Table 15*). For people aged  $< 55$  years, we observed an estimate mean change of 15.4 points on the WAB-AQ, followed by an estimate mean change of 12.4 points for people aged 56–65 years (see *Table 8*). Similarly, for people enrolled in RCTs within 0–1 month of stroke, the estimate mean change was 19.1 points; for those enrolled within 1–3 months of stroke, the estimate mean change was 16.2 points. This could reflect the influence of spontaneous recovery in the early stages after stroke. Although the groupings by age and time since stroke were not significant at a multivariable level, the observed changes in language ability since baseline were notable and may require further study.

When analysing data from all study types, similar results were observed; time group became significantly negatively associated with improvement in overall language ability ( $p = 0.0098$ ). Enrolment within 28 days of index stroke was associated with an estimate mean change of 21.0 points on the WAB-AQ, whereas enrolment within 1–3 months of stroke was associated with an estimate mean change of 16.4 points on the WAB-AQ (see *Table 8*).

### Auditory comprehension

A total of 556 IPD from 16 RCTs had auditory comprehension data at baseline and follow-up, but only 550 IPD had both baseline and follow-up auditory comprehension analysis, relevant demographic data and a SLT intervention to support the planned analysis (see *Appendix 8, Table 15*).

### Demographic analysis

The values in the 'change from baseline' variable were not normally distributed (skewed). When modelled using the baseline score as a linear function of the 'change from baseline', the residuals were reasonably normally distributed. Thus the 'change from baseline' values remained untransformed. As with measures of overall language ability, baseline auditory comprehension scores were positively associated with change at first follow-up ( $p < 0.0001$ ). At univariable level, age was also inversely significantly associated with recovery ( $p = 0.003$ ). This association remained strong when baseline score was controlled for. Auditory comprehension scores at baseline were significantly associated with change in scores at follow-up in multivariable analyses and age (grouped) ( $p = 0.002$ ) (see *Appendix 8, Table 15*).

Although sex and time since stroke were not significant predictors in the model (see *Appendix 8, Table 15*), we included them in the analysis together with age. We considered differences between studies and changes in magnitude of effect to inform the later stages of the planned analyses. We observed little difference on measures of auditory comprehension between female and male participants [female estimate mean 3.8 points (95% CI 0.98 to 6.66 points) vs. male estimate mean 3.1 points (95% 0.35 to 5.85 points)]. We also observed greater improvements among younger participants and those in the early months after aphasia onset ( $p = 0.047$ ); those aged  $< 55$  years had an estimate mean change of 6.05 (95% CI 3.12 to 8.94) points on the TT-AAT. The inclusion of non-RCT data supported these findings (see *Table 8*).

### Naming

We identified 13 RCT data sets involving 391 IPD with naming measures available at baseline and follow-up. Six participants who received a social support intervention were excluded; therefore, the naming analysis was based on 385 IPD (13 RCTs; see *Appendix 8, Table 15*).

### Demographic analysis

Although the data on changes from baseline were skewed, the residuals from the model with baseline were normally distributed, and so the change value remained untransformed. Only English and Dutch languages were languages of data collection in more than one trial; although this made language of data collection a candidate for a subset analysis comparing languages, there were no within-study comparisons of language, meaning that the significant results should be interpreted with caution (see *Appendix 8, Table 15*). There was a trend towards a difference between age groups; because age, time since stroke and sex are typically considered in studies of stroke recovery and rehabilitation, they were included in our model to account for population differences.

An earlier time point for study enrolment (and subsequent follow-up) was associated with a higher impact on change in naming scores [estimated mean change of 11.12 points (95% CI 5.7 to 16.5 points) on the BNT] than interventions at 3–6 months after stroke, for which the mean change was non-significant (estimated mean change of 4.3 points, 95% CI  $-1.6$  to 10.1 points) (see *Table 8*). Although the time group for intervention was not significant, the point estimates indicate that these trends may warrant further examination. Early intervention after stroke appeared to have the highest impact on change (with spontaneous recovery possibly contributing to recovery profile in the early phases post stroke), as did younger age, with people aged  $< 55$  years estimated to change by 9.31 points on the BNT (95% CI 4.7 to 13.9 points), whereas older age groups had a non-significant change of 4.42 points (see *Table 8*).

### Other spoken language

Three RCTs (182 IPD) and three non-RCT data sets (49 IPD) reported other spoken-language outcome measures. The data were transformed to the anchor measures (PICA with a scale of 0–16). There were too few comparisons using RCT data sets only, and so we report an analysis that was inclusive of all data sets (see *Appendix 8, Table 15*). Other spoken language scores by time and age group at baseline were significantly associated with change in scores at follow up in multivariable analyses age (group  $p = 0.015$ ) and time since stroke (group  $p = 0.01$ ) (see *Appendix 8, Table 15*).

### Demographic analysis

All participants from baseline to their first follow-up after the end of treatment (when there were multiple options) were included (231 IPD; 6 data sets). As the baseline score was not a statistically significant predictor of 'change from baseline', we did not conduct a bivariate (baseline plus other predictive variable) analysis as we did for other domains reported in this section (see *Appendix 8, Table 15*).

Intervention within the first 3 months of index stroke significantly benefited spoken-language outcomes (estimated mean change of 1.9 points on the spoken-language PICA 16-point scale) compared with study enrolment > 6 months after stroke (non-significant mean change; see *Table 8*).

### Reading comprehension

Only one RCT (11 IPD) reported reading outcomes, and so the following analyses were performed on that RCT and three non-RCT data sets (77 IPD) with reading data on participants at baseline and follow-up (see *Table 8*). All data (88 IPD; 4 data sets) were transformed to the CAT reading subtest (scale of 0–74).

### Demographic analysis

Residuals were skewed and so the change from baseline in the following sections (see *Appendix 8, Table 15*) has been transformed on the log scale.

Interventions delivered earlier after stroke (between 4 weeks and 3 months since stroke) were associated with the greatest benefits of intervention on measures of reading comprehension (4.0 points on the CAT; see *Table 8*), possibly due, in part, to spontaneous recovery after stroke. As for other variables, younger age groups (< 55 years of age) benefited most, with a mean change of 5.5 points on the reading comprehension outcome (see *Table 8*).

### Writing

On review of the data, we identified three RCTs (47 IPD) that reported data on writing at baseline and at a subsequent follow-up time point (see *Appendix 8, Table 15*). No non-RCT data sets provided writing data at these time points. All writing data were transformed to the anchor measures (the CAT with a scale of 0–76).

### Demographic analysis

We analysed participants from baseline to the first follow-up after the end of treatment (when there were multiple options). Neither the data on change from baseline nor the residual values were skewed; thus, the change value remained untransformed. As the baseline writing score was not significant, we did not conduct a bivariable analysis as we did for other domains reported in this section (see *Appendix 8, Table 15*).

Early intervention (between 4 weeks and 3 months) was associated with a mean benefit of 7.8 points on writing domain outcomes (95% CI 2.3 to 13.4 points on the CAT writing subtest). No other significant changes were noted for other time points after stroke (see *Table 8*).

### Functional communication

Functional communication was captured using three distinct measurement approaches: (1) tools that captured data using an observer-rated approach, (2) tools that asked participants to self-rate their functional communication abilities and (3) discourse analysis approaches that captured and quantified the presence of particular language or communicative features in a defined sample of language. Measures captured using the three different approaches could not be meta-analysed across approaches, and are thus analysed and presented separately.

### Functional communication: observer-rated measures

A total of 14 RCTs (544 IPD) that reported functional communication using observational measures at baseline and at a subsequent post-intervention time point were identified. An additional five non-RCT data sets (115 IPD) provided additional functional communication data at these time points (see *Table 8*).

### Demographic analysis

We analysed participants from baseline to the first follow-up after the end of treatment. For one measure [the Therapy Outcome Measure (TOM)], two subtests (activity or participation) were used in a single RCT capturing data on the same participants. For our purposes, either subtest could be included in the functional communication meta-analysis. Both were equally valid inclusions. We arbitrarily included the activity subtest data (see *Appendix 8, Table 15*) and conducted a sensitivity analysis to examine whether or not there was any change in the findings had we included the participation subtest data (reported in *Appendix 9, Tables 16–17*).

Using the activity subtest data from the TOMs, we found that the data on change from baseline were skewed, but the residuals from the model with baseline were reasonably normally distributed, and so the change value remained untransformed. Time since stroke was significant in univariable and multivariable analyses (see *Appendix 8, Table 15*). Age and sex were significant in the participant subset with complete data. All three variables were retained in the basic model.

Eleven participants did not have information on their time since stroke in a suitable format for data synthesis and were excluded from the analysis; therefore, the effective sample size from RCT data set was 533 IPD (see *Table 8*). Female participants had higher mean observational scores than male participants (mean 0.76, 95% CI 0.48 to 1.0, on the AAT-SSC), and the youngest participants (< 55 years of age) had higher mean scores (mean 0.75, 95% CI 0.46 to 1.0, on the AAT-SSC) than older age groups. Similarly, participants within 1 month of aphasia onset had a mean score of 1.05 on the AAT-SSC (95% CI 0.70 to 6.99), compared with participants who were > 6 months after aphasia onset (mean 0.33, 95% CI 0.00 to 0.66; see *Table 8*). The findings based on the non-RCT IPD supported those found above (see *Table 8*).

### Functional communication: self-rated measures

There were insufficient data (11 IPD; 1 data set with baseline and follow-up data) to support the analysis of univariable and multivariable relationships to functional communication as rated by people with aphasia. Inclusion of the non-RCT data did not change the feasibility of the planned analysis (43 IPD; 2 data sets).

### Discourse analysis

Discourse analysis data were similarly sparse (423 IPD; 5 data sets), with limited overlap in the method of data sampling and data items recorded. We were unable to synthesise these data to support the planned analysis of univariable and multivariable relationships.

## Summary

Age was significantly associated with change in absolute percentage score across selected domains and time since stroke was significantly associated with absolute proportion of change since baseline across all language domains. These variables will be taken forward to be included in statistical base models in subsequent analyses, when appropriate, in *Chapter 6*. Across each of the multivariable analyses, baseline language domain score, age, sex and time since stroke were selectively significantly associated with absolute change in the raw language domain scores.

Further to the observations of time having a significant association with change in selected domain scores at follow-up, we observed that, across all language domains, the highest absolute change in scores from baseline were seen in those participants enrolled in a study within 1 month of index stroke and those who were aged < 55 years. Females also appeared to have a trend towards better recovery on measures of overall language ability and functional communication than males.



# Chapter 6 Optimising speech and language therapy interventions for aphasia after stroke

## Overview

We examined the impact of the modifiable components of SLT interventions for aphasia after stroke (e.g. regimen, intervention approach and delivery; see *Table 1* and *Box 3*). We included age, time since aphasia onset and sex to account for population differences between data sets, in advance of the planned network meta-analysis considering the impact of intervention variables. These factors are considered important predictors of general stroke recovery and were important predictors for language recovery in the preceding analysis across selected language domains for absolute changes in raw scores from baseline to first follow-up (see *Chapters 4* and *5*).

We considered language measures at first follow-up after SLT intervention periods. Data sets and IPD filtering in preparation for analysis were reported in *Table 5*. We explored the impact of SLT intervention by regimen, therapy approach, delivery model and tailoring. When a SLT intervention variable was reported for an isolated data set only, then the effect of that variable on language could not be distinguished from the study effect, and findings were treated with caution.

## Network meta-analysis

Each SLT intervention variable was considered simultaneously (with continuous dose variables such as frequency grouped) in the context of language recovery (overall language ability, auditory comprehension, naming and functional communication). There were insufficient data to consider the impact of SLT variables on other spoken language, reading comprehension, writing or functional communication (self-rated) domains (see *Table 5*). The following analysis presents the overall language ability, auditory comprehension, naming and functional communication (observer-rated) findings (see *Appendices 11–14*).

The functional communication domain includes data gathered on the TOMs, when subtest data on communication activity or participation were available. We arbitrarily included the TOMs activity data set in the main analysis, but conducted a sensitivity analysis, repeating the analysis inclusive of the participation data to consider whether or not our decision had affected the findings (see *Appendix 9*, *Tables 16–18*, and *Chapter 8*).

Within-study clustering was examined for the four language domains and the four treatment regimen categories: frequency, duration, intensity and dosage (see *Appendix 15*, *Table 19*). This form of structuring of the data, which allows for correlation between patients within studies, did not significantly improve the fit of our predictive model to the data. The additional modelling of within study clustering was either non-significant or caused the failure of the analysis due to the G matrix not being positive definite (see *Appendix 15*, *Table 19*).

We examined the contribution to the model (which included baseline score, sex, age group and time since stroke) of each SLT intervention by regimen (frequency, duration, intensity, dosage, home practice), intervention approach (impairment target, theoretical approach) and delivery (provider expertise, context, tailoring by functional relevance and difficulty). We explored the magnitude of differences seen with different degrees of the SLT component of interest (e.g. providing 5 or 14 or 20 hours of SLT; see overview in *Appendix 16*, *Table 20*).

## Frequency of speech and language therapy for aphasia

We started with a base model that included the language domain absolute raw score as the outcome, and age, sex and time since stroke as covariates. We added frequency of SLT (i.e. the number of days per week that SLT was delivered) to this model and assessed its impact on language domain scores. Frequency, in addition to age, sex and time since stroke, significantly contributed to auditory comprehension ( $p = 0.0091$ ) and naming ( $p = 0.03$ ) outcomes, but not to overall language ability or functional communication outcomes (see *Report Supplementary Material 5*). We saw significant improvements in participants' scores from baseline to first follow-up across overall language ability, auditory comprehension, naming and functional communication language domains. Data on reading outcomes were absent from included RCTs (see *Appendix 17, Table 21*). Based on RCT IPD, the greatest overall language ability [14.95 points (95% CI 8.67 to 21.23 points) on the WAB-AQ (194 IPD; 6 RCTs)] and functional communication gains [0.78 points (95% CI 0.48 to 1.09 points) on the AAT-SSC (155 IPD; 8 RCTs)] occurred alongside delivery of SLT 4 to 5 days weekly. The highest auditory comprehension gains [5.86 points (95% CI 1.64 to 10.01 points) on the TT-AAT (114 IPD; 5 RCTs)] were associated with receiving SLT 3 to 4 days weekly. The greatest naming gains [12.05 points (95% CI 6.52 to 17.59 points) on the BNT (42 IPD; 3 RCTs)] occurred alongside receiving SLT up to 2 days weekly, but this was based on small numbers of IPD and RCTs, and a network geometry with limited connections; therefore, caution should be used when interpreting this finding (see *Appendix 13, Figure 31*). The non-RCTs IPD supported these findings (see *Appendix 17, Table 21*).

## Duration of speech and language therapy for aphasia

Speech and language therapy duration reflected the total number of weeks that the intervention lasted. The addition of the duration variable to the base model was significantly associated with auditory comprehension outcomes ( $p = 0.0013$ ; see *Report Supplementary Material 6*), but not with other domains. Importantly, the SLT duration network meta-analysis geometry was unstable, with few studies comparing therapy durations and little variation on maximum gains in the context of SLT of different durations (see *Appendices 11–14 and 18*); thus, the SLT duration findings should be interpreted with caution. The greatest gains on overall language ability [17.27 points (95% CI 9.71 to 24.82 points) on the WAB-AQ (45 IPD; 3 RCTs)] and auditory comprehension [6.79 points (95% CI 1.69 to 11.88 points) on the TT-AAT (93 IPD; 5 RCTs)] were associated with SLT lasting 10–20 weeks. Naming gains from baseline were greatest [8.38 points (95% CI 1.24 to 15.51 points) on the BNT (134 IPD; 3 RCT)] alongside > 20 weeks of SLT. The best gains in functional communication [0.8 points (95% CI 0.29 to 1.31 points) on the AAT-SSC (57 IPD; 2 RCTs)] occurred with 4–10 weeks of SLT (see *Appendix 18, Table 22*). Non-RCT data were generally confirmatory (see *Appendix 18, Table 22*).

## Intensity of speech and language therapy for aphasia

Intensity of SLT was measured by the number of SLT hours delivered weekly. Including the intensity variable in the base model (with age, sex and time since stroke) significantly contributed to auditory comprehension outcomes ( $p = 0.0004$ ), but not to any other domains (see *Report Supplementary Material 7*). Although clinically similar gains occurred alongside different SLT intensities, peak gains on overall language ability [15.85 points (95% CI 8.06 to 23.64 points) on the WAB-AQ (74 IPD; 3 RCTs)], naming [13.23 points (95% CI 5.83 to 20.64 points) on the BNT (18 IPD; 2 RCTs)] and functional communication [0.77 points (95% CI 0.36 to 1.19 points) on the AAT-SSC (83 IPD; 4 RCTs)] were all associated with receiving SLT for up to 2 hours weekly. In contrast, peak auditory comprehension gains [7.3 points (95% CI 4.09 to 10.52 points) on the TT-AAT (141 IPD; 6 RCTs)] occurred when delivery of SLT was in excess of 9 hours weekly. The non-RCT data set provided similar findings (see *Appendix 19, Table 23*).

## Dosage of speech and language therapy for aphasia

Including the SLT dosage variable (total number of SLT hours) to the base model of age, sex and time since stroke significantly contributed to naming ( $p = 0.040$ ) and functional communication ( $p = 0.018$ ) outcomes, but not to other domains (see *Report Supplementary Material 8*).

The greatest gains in overall language ability [18.37 points (95% CI 10.58 to 26.16 points) on the WAB-AQ (31 IPD; 4 RCTs)] and auditory comprehension [5.23 points (95% CI 1.51 to 8.95 points) on the TT-AAT (90 IPD; 7 RCTs)] were associated with 20–50 hours of SLT. Functional communication gains [0.94 points (95% CI 0.34 to 1.55 points) on the AAT-SSC (11 IPD; 3 RCTs)] were highest in the context of a slightly lower SLT dosage of 14–20 hours. Naming gains were highest alongside up to 5 hours of SLT [12.48 points (95% CI 1.34 to 23.63 points) on the BNT (28 IPD; 2 RCTs)] (see *Appendix 20, Table 24*). For functional communication and naming gains, IPD and RCT numbers were low and the naming network analysis geometry was unstable (see *Appendix 13, Figure 31*). It is noteworthy that, for both functional communication and naming, the second-highest gains occurred in the context of 20–50 hours of SLT [naming: 9.23 points (95% CI 1.75 to 16.7 points) on the BNT (81 IPD; 5 RCTs); functional communication: 0.77 points (95% CI 0.43 to 1.1 points) on the AAT-SSC (96 IPD; 9 RCTs)] (see *Appendix 20, Table 24*). Addition of the non-RCT IPD was generally confirmatory, although the greatest (and only significant) naming gains from baseline [11.32 points (95% CI 5.92 to 16.72 points) on the BNT (135 IPD; 8 data sets)] were associated with 20–50 hours of SLT (see *Appendix 20, Table 24*).

## Home practice

Prescribed SLT home practice augments face-to-face therapy dosage. Included data sets rarely described home practice dosage, so we considered whether or not data sets reported the prescription of home practice (yes/no). When home practice was not reported, we assumed that it was not present. Adding the home practice variable to the base model (sex, age, time since stroke) significantly contributed to auditory comprehension outcomes ( $p = 0.019$ ; see *Report Supplementary Material 9*), but not to other language domains. The best gains from baseline on overall language ability [16.69 points (95% CI 10.01 to 23.37 points) on the WAB-AQ (87 IPD; 2 RCTs)] and auditory comprehension [5.28 points (95% CI 2.19 to 8.37 points) on the TT-AAT (278 IPD; 7 RCTs)] were associated with prescribed home practice. In contrast, naming gains [7.08 points (95% CI 1.81 to 12.35 points) on the BNT (166 IPD; 9 RCTs)] and functional communication gains [0.74 points (95% CI 0.39 to 1.09 points) on the AAT-SSC (267 IPD; 10 RCTs)] were slightly higher in RCTs that did not report home practice than in those that did. Including the non-RCT data generally confirmed these findings, except for functional communication, when greater gains were achieved by the group for which home practice was reported [0.69 points (95% CI 0.34 to 1.04 points) on the AAT-SSC (187 IPD; 5 RCTs)] than by the group for which home practice was not reported (see *Appendix 21, Table 25*).

## Speech and language therapy regimen

We considered the contribution that unit increases in the SLT intervention regimen (frequency, duration, dosage and intensity) made to specific language outcomes using simple linear regression models and using the IPD RCT data set only (*Table 9*). For example, for every unit increase in SLT intensity (i.e. every additional SLT hour weekly), the average overall language ability score change from baseline was an increase of 0.23 points on the WAB-AQ. These average changes by regimen, language domain and anchor measure are presented in *Table 9*. Examination of the categorical data suggests that excess treatment may have a negative effect on participants in some domains. Naming scores appear to be negatively affected by increased SLT frequency, intensity and dosage; thus, further examination of SLT regimen in the context of network meta-analyses is required. Changes from baseline may have been reduced in the higher-dose bandings.

TABLE 9 Increase in language performance<sup>a</sup> score by unit increase in SLT regimen

SLT regimen	Estimate (slope) [SE]	Intercept [SE]
<b>Frequency of SLT (days per week)</b>		
Overall language ability (WAB-AQ)	0.58 [0.37]	18.19 [5.10]
Auditory comprehension (TT-AAT)	0.57 [0.24]	2.86 [2.25]
Naming (BNT)	-0.87 [0.37]	5.38 [3.21]
Functional communication (AAT-SSC)	0.28 [0.11]	2.63 [1.06]
<b>Duration of SLT (total weeks)</b>		
Overall language ability (WAB-AQ)	0.06 [0.09]	19.19 [4.92]
Auditory comprehension (TT-AAT)	-0.29 [0.07]	6.75 [2.33]
Naming (BNT)	0.03 [0.08]	2.56 [3.16]
Functional communication (AAT-SSC)	0.04 [0.03]	3.08 [1.06]
<b>Intensity of SLT (hours per week)</b>		
Overall language ability (WAB-AQ)	0.23 [0.26]	18.61 [5.00]
Auditory comprehension (TT-AAT)	0.30 [0.11]	2.66 [2.27]
Naming (BNT)	-0.21 [0.16]	4.13 [3.26]
Functional communication (AAT-SSC)	0.06 [0.06]	2.96 [1.16]
<b>Dosage of SLT (total hours)</b>		
Overall language ability (WAB-AQ)	0.02 [0.03]	19.82 [4.89]
Auditory comprehension (TT-AAT)	0.01 [0.02]	4.60 [2.22]
Naming (BNT)	-0.07 [0.03]	5.51 [3.50]
Functional communication (AAT-SSC)	0.03 [0.01]	2.64 [0.98]
SE, standard error.		
a Insufficient data on other spoken language, reading comprehension, writing or functional communication (self-rated).		
<b>Note</b>		
WAB-AQ range: 0–100; TT-AAT range: 0–50; BNT range: 0–50; AAT-SSC range: 0–5.		

## Target of speech and language therapy intervention

Including the SLT target variable in the base model did not significantly contribute to the language outcomes (see *Report Supplementary Material 10*). Few significant gains from baseline were observed. The greatest gains in overall language ability [15.62 points (95% CI 8.82 to 22.43 points) on the WAB-AQ (245 IPD; 8 RCTs)] and functional communication [1.05 points (95% CI 0.52 to 1.58 points) on the AAT-SSC (72 IPD; 3 RCTs)] were associated with mixed SLT approaches (see *Appendix 22, Table 26*). The greatest gains in auditory comprehension [4.46 points (95% CI 0.31 to 8.62 points) on the TT-AAT (136 IPD; 7 RCTs)] and naming [8.82 points (95% CI 3.15 to 14.49 points) on the BNT (174 IPD; 7 RCTs)] were associated with word-finding SLT. The inclusion of non-RCT data was generally confirmatory (see *Appendix 22, Table 27*).

## Theoretical approach of speech and language therapy intervention

Including the SLT theoretical approach variable in the base model of age, sex and time since stroke did not significantly contribute to the model on any language domain (see *Report Supplementary Material 11*).

The numbers of IPD, data sets and network connections were generally low (see *Appendices 11–14*); therefore, the data were unreliable, and findings should be considered cautiously. Few significant gains from baseline were observed. When the greatest gains were identified, overall language ability [20.39 points (95% CI 1.90 to 38.88 points) on the WAB-AQ (60 IPD; 2 RCTs)] and auditory comprehension gains [11.93 points (95% CI 1.44 to 22.43 points) on the TT-AAT (35 IPD; 1 RCT)] were associated with semantic–phonological SLT approaches. Functional/pragmatic approaches were associated with the greatest functional communication gains [1.82 points (95% CI 0.36 to 3.28 points) on the AAT-SSC (8 IPD; 1 RCT)] (see *Appendix 23, Table 27*).

Adding multimodal approaches to the base model together with age, sex and time since stroke significantly contributed to functional communication outcomes, but not to any other outcome (see *Report Supplementary Material 12*). Functional communication gains (as measured by the AAT-SSC) were observed in the context of multimodal approaches [verbal: 1.96 points, 95% CI 0.85 to 3.07 points (38 IPD; 2 RCTs); total: 1.90 points, 95% CI 0.86 to 2.93 points (66 IPD; 3 RCTs)] and verbal SLT approaches [1.95 points, 95% CI 0.92 to 2.99 points (273 IPD; 10 RCTs)] (see *Appendix 24, Table 28*). No significant gains from baseline were observed in the context of multimodal SLT (verbal or total) on auditory comprehension or naming (see *Appendix 24, Table 28*).

## Expertise

We categorised the expertise of the person delivering SLT as either professional (therapist or researcher) or non-professional (trained volunteer or family member). Adding the expertise variable to the base model of age, sex and time since stroke did not significantly contribute to any outcomes (see *Report Supplementary Material 13*). The availability of IPD based on non-professional-delivered SLT interventions was poor (< 15 IPD across the language domains), and findings should be interpreted with caution (see *Appendix 25, Table 29*). Inclusion of the non-RCT data did not alter these findings.

## Context of delivery

The SLT context (whether participants were inpatients or outpatients during their therapy sessions) was extracted. Adding this variable to the model of age, sex and time since stroke did not make a significant contribution to language outcomes when based on IPD from RCTs or non-RCT data (see *Report Supplementary Material 14*). The SLT context made little impact on the gains made from baseline (see *Appendix 26, Table 30*).

## Mode of delivery

We considered the SLT delivery mode as either face to face, computer supported or self-managed. Adding the delivery mode variable to the base model did not significantly contribute to the language outcomes (see *Report Supplementary Material 15*).

Overall, we observed some slight, but clinically insignificant, difference in gains between face-to-face SLT and non-face-to-face approaches, for example overall language ability (as measured on the WAB-AQ) gains associated with face-to-face SLT (14.13 points, 95% CI 8.34 to 19.91 points) versus non-face-to-face SLT (11.06 points, 95% CI 2.63 to 19.49 points) (351 IPD; 11 RCTs) (see *Appendix 27, Table 31*).

## Tailoring

The content of a SLT intervention may be tailored to an individual patient's needs in two ways: tailoring by functional relevance and/or tailoring by level of language difficulty. When tailoring was not reported, we assumed that it had not taken place. There were no within-study comparisons of tailored and untailored approaches.

### *Tailoring by functional relevance*

The addition of the tailoring by functional relevance variable to the base model significantly contributed to auditory comprehension outcomes ( $p = 0.029$ ), but not to other domains (see *Report Supplementary Material 16*).

When significant changes were observed, higher gains occurred in the context of functionally relevant SLT for overall language ability [16.47 points (95% CI 10.95 to 21.99 points) on the WAB-AQ (232 IPD; 6 RCTs)], naming [8.79 points (95% CI 1.95 to 15.63 points) on the BNT (113 IPD; 5 RCTs)] and functional communication [0.74 points (95% CI 0.38 to 1.10 points) on the AAT-SSC (249 IPD; 6 RCTs)] than with non-tailored SLT interventions. Similarly, significant gains from baseline for auditory comprehension were only evident in the context of SLT tailored by functional relevance [5.26 points (95% CI 2.05 to 8.47 points) on the TT-AAT (194 IPD; 7 RCTs)] (see *Appendix 28, Table 32*). The analysis inclusive of IPD from non-RCTs confirmed these findings.

### *Tailoring by difficulty*

Including the SLT tailoring by difficulty variable in the base model significantly contributed to auditory comprehension outcomes ( $p = 0.043$ ), but not to any other language outcome. Inclusion of the non-RCT data supported this finding (see *Report Supplementary Material 17*).

Tailoring of SLT by difficulty was associated with higher gains in overall language ability [14.46 points (95% CI 8.82 to 20.09 points) on the WAB-AQ (210 IPD; 7 RCTs)] than was untailored SLT [13.24 points (95% CI 7.50 to 18.99 points) on the WAB-AQ (207 IPD; 6 RCTs)], but this difference is not clinically relevant. In contrast, auditory comprehension gains from baseline were only significant in the context of SLT tailored for level of difficulty [4.57 points, 95% CI 1.55 to 7.60 points (331 IPD; 10 RCTs)] as participants receiving SLT untailored by level of language difficulty made no significant gains (see *Appendix 29, Table 33*).

In contrast, SLT untailored to participants' levels of language difficulty was associated with higher gains in naming [10.21 points (95% CI 2.75 to 17.67 points) on the BNT (79 IPD; 4 RCTs)] and functional communication [0.81 points (95% CI 0.34 to 1.27 points) on the AAT-SSC (141 IPD; 5 RCTs)] than tailored SLT (see *Appendix 29, Table 33*). The non-RCT data supported these findings.

## Heterogeneity

We considered heterogeneity with reference to risk of selection bias, study variability and methodological quality.

We examined the similarity of participant groups in the primary data sets (RCTs and non-RCTs) at baseline, comparing participants' age, sex, time since stroke, aphasia severity, handedness and years of education (when available), and they were broadly similar (see *Appendices 4 and 5*).

Speech and language therapy interventions included in the analysis differed between intervention groups and across studies, but there was consensus that all were SLT interventions. Variations in SLT approaches (by delivery, intervention approach and regimen) were explored in the analysis.

The early pilot analysis resulted in unacceptably high relative study variability, in excess of 25%. Following careful examination of the contributing data sets and groupings in this analysis (e.g. the dose thresholds), data set checks and a minor adjustment to the algorithm (see *Appendix 2, Box 4*), the variance subsequently lay between 10% and 25% and all remained under 30%. Higher variance values observed were considered to be related to small IPD in some cells. No analysis exceeded the prespecified threshold of 50% relative variability due to study differences.

## Summary

Having established a base model of the language domain absolute raw scores as outcomes, and age, time since stroke and sex as covariates, we included SLT intervention parameters in succession. We found that several SLT intervention parameters significantly contributed to selective language domain outcomes: auditory comprehension and SLT frequency, intensity, home practice and tailoring (by functional relevance and difficulty); naming and SLT frequency and dosage; and functional communication and SLT dosage. The addition of SLT impairment target, provider's expertise, the mode of SLT and therapy context to the base model made no significant contribution to language outcomes.

The greatest gains across language outcomes were observed in the context of SLT regimens that varied by frequency, intensity and dosage; these are summarised in *Chapter 8*. Duration and naming data were treated with caution across all language domains because of unstable network geometry and, in many cases, small numbers of IPD and data sets.

Overall language ability gains were highest in the context of receiving SLT 4 to 5 days weekly, for up to 2 hours weekly and over 20–50 hours in total, using mixed expressive and receptive language impairment approaches, tailored to the participant (by functional relevance and level of difficulty) and with prescribed home practice tasks.

The highest auditory comprehension gains were associated with receiving SLT 3 days weekly, for > 9 hours weekly, for a total of 20–50 hours, tailored to the participant (by functional relevance and level of difficulty) word-finding SLT approaches augmented with prescribed home practice tasks.

Participants' functional communication gains were best in the context of receiving SLT 4 to 5 days weekly, for up to 2 hours weekly, for 14–50 hours in total, using functionally relevant approaches, targeting expressive and receptive language impairment (mixed SLT). The mode of delivery (face to face, computer supported or self-managed) and the context of SLT (inpatient vs. outpatient settings) made little clinical difference to the language gains observed from baseline. As planned, variability in language outcome gains and the SLT context in which they occur was further explored by participant subgroups (age, sex, time since stroke and aphasia severity), and is reported in *Chapter 7*.



# Chapter 7 Speech and language therapy interventions for subgroups of people with aphasia

## Overview

We undertook prespecified subgroup analyses to explore language change in the context of SLT frequency, duration, intensity and dosage, and whether or not the findings varied by participants' age, time since aphasia onset and aphasia severity. Building on the preceding results (see *Chapters 4–6*), the post hoc subgroup analysis also considered whether or not language gains made by males and females varied in the context of different SLT interventions. Reflecting IPD availability, we restricted these subgroup analyses to four language domains (overall language ability, auditory comprehension, naming and functional communication) and to IPD from RCT data sets only. We considered data set variability for each analysis.

## Speech and language therapy and language outcomes by subgroup

Subgroup analyses were conducted using IPD network meta-analysis (see *Chapter 6*) to evaluate participants' language gains according to baseline criteria: age, time since aphasia onset and stroke severity. In the context of the observations in relation to language recovery and sex (*Chapters 4–6*) and the known relationship between sex and other stroke outcomes, we included a post hoc comparison between female and male participants' responses to SLT on language outcomes.

We had functional communication (observer-rated) data from some participants on the TOMs activity and participation subtests. Previously, we found no indication that the choice of which TOMs subtest to include in the analysis affected the findings (see *Chapter 6* and *Appendix 9, Tables 16–18*). Thus, we conducted the subgroup analysis inclusive of the TOMs activity data only.

We dichotomised RCT participants based on their median baseline language score, age ( $\pm 65$  years), time since aphasia onset at baseline ( $\pm 3$  months) and sex. To represent the entire database population, median baseline language scores were calculated from all RCT and non-RCT IPD, regardless of the availability of SLT regimen or follow-up data. Age, however, was dichotomised, to reflect the age groups used earlier in the analysis ( $\leq 65$  years and  $> 65$  years; see *Chapters 5* and *6*) rather than the median of all IPD (which was 63 years; see *Chapter 3*).

We considered relative variance, highlighting analyses where it exceeded 25%. We report variance that exceeded 50% in the tables for completeness, but we do not include such results when reporting the findings. Across the subgroups (and when significant changes from baseline were observed), generally we continued to see the highest gains in language performance from baseline among the participants aged  $< 65$  years, females and those who received SLT within 3 months of the index stroke (*Table 10*).

## Age

We investigated whether or not the younger ( $\leq 65$  years; 277 IPD) and older participants' ( $> 65$  years; 205 IPD) language recoveries differed in the context of SLT variations. Relative variance was modest ( $< 50\%$ ) across comparisons.

TABLE 10 Base model subgroups by greatest significant improvements

Characteristic	Language domain	Age (years)		Time since aphasia onset		Aphasia severity at baseline		Sex	
		Young ( $\leq 65$ )	Old ( $> 65$ )	Early ( $\leq 3$ months post onset)	Late ( $> 3$ months post onset)	Mild-moderate	Moderate-severe	F	M
Age (years)	Overall language ability			$\leq 55$	$\leq 55$	$\leq 65$	$\leq 55$	$\leq 55$ and $> 75$	$\leq 55$ and $> 75$
	Auditory comprehension			$\leq 55$	$\leq 55$	NS	$\leq 55$	56 to 65	$\leq 55$
	Naming			$\leq 55$	$\leq 65$	$\leq 75$	$\leq 65$	$\leq 55$	$\geq 55$
	Functional communication			$\leq 55$	NS	NS	$> 56$ to 65	56 to 65	$> 75$
Time since stroke onset (months)	Overall language ability	$\leq 3$	$\leq 1$			$\leq 1$	$\leq 3$	$\leq 1$	$\leq 1$
	Auditory comprehension	$\leq 1$	$\leq 3$			NS	$\leq 3$	$\leq 3$	$\leq 3$
	Naming	$\leq 1$	$\leq 1$			$\leq 1$	$\leq 1$	$\leq 1$ to 3	$\leq 1$
	Functional communication	$\leq 1$	$\leq 1$			$\leq 1$	$\leq 1$	$\leq 1$ to 3	$\leq 1$
Sex	Overall language ability	F = M	F $>$ M	F $>$ M	F $>$ M	F = M	F $>$ M		
	Auditory comprehension	F $>$ M	F = M	NS	F $>$ M	NS	M $>$ F		
	Naming	F $>$ M	NS	M $>$ F	F $>$ M	F = M	F = M		
	Functional communication	F $>$ M	F $>$ M	F $>$ M	NS	NS	F $>$ M		

F, female; M, male; NS, non-significant change observed.

**Note**

Blue font indicates 35–50% relative variability; red font indicates  $> 50\%$  relative variability.

### Age and speech and language therapy frequency

Younger participants gained most on overall language ability (measured on the WAB-AQ) in the context of SLT 5 or more days weekly [15.12 points, 95% CI 8.15 to 22.08 points (107 IPD; 6 RCT)], and older participants gain most when they received SLT more than 5 days weekly [17.19 points, 95% CI 3.85 to 30.53 points (10 IPD; 2 RCT)]. Younger and older participants' auditory comprehension (measured on the TT-AAT) made the best gains when SLT occurred 4 or more days weekly [young: 6.78 points, 95% CI 2.33 to 11.22 points (64 IPD; 5 RCTs); old: 8.48 points, 95% CI 2.04 to 14.93 points (50 IPD; 3 RCTs)]. Similarly, both groups made the highest naming gains (measured on the BNT) in the context of receiving SLT up to 2 days weekly [young: 15.02 points, 95% CI 8.95 to 21.10 points (26 IPD; 4 RCTs); old: 9.83 points, 95% CI 2.44 to 17.22 points (16 IPD; RCTs 4)]. Younger participants gained most functional communication (measured on the AAT-SSC) alongside SLT occurring more than 5 days weekly [1.18 points, 95% CI 0.28 to 2.08 points (but based only on 3 IPD; 2 RCTs)], whereas the older group gained most when SLT occurred at least 4 or 5 days weekly [0.78 points, 95% CI 0.15 to 1.40 points (54 IPD; 3 RCTs)] (see *Appendix 30, Table 34*, and *Appendix 34, Table 38*).

### Age and speech and language therapy duration

The younger group's greatest overall language [22.69 points (95% CI 15.20 to 30.19 points) on the WAB-AQ (25 IPD; 3 RCTs)], auditory comprehension [8.41 points (95% CI 2.62 to 14.20 points) on the TT-AAT (60 IPD; 5 RCTs)] and naming gains [11.27 points (95% CI 5.44 to 17.11 points) on the BNT (59 IPD; 4 RCTs)] were associated with between 10 and 20 weeks of SLT. In contrast, the older participants' greatest gains in overall language [20.60 points (95% CI 7.77 to 33.42 points) on the WAB-AQ (15 IPD; 2 RCTs)] and naming [11.23 points (95% CI 2.03 to 20.43 points) on the BNT (71 IPD; 3 RCTs)] occurred when SLT lasted for > 20 weeks. We found no evidence of significant auditory comprehension gains for the older group (see *Appendix 30, Table 34*, and *Appendix 34, Table 38*).

### Age and speech and language therapy intensity

Younger participants made the best overall language ability [16.97, 95% CI 9.96 to 23.98 (78 IPD; 3 RCTs)] and auditory comprehension gains [8.96 points, 95% CI 5.35 to 12.56 points (108 IPD; 4 RCTs)] alongside > 9 hours of SLT weekly. Although the older group's best auditory comprehension gains were also associated with > 9 hours of SLT weekly [5.34 points (95% CI 0.67 to 10.02 points) on the TT-AAT (33 IPD; 6 RCTs)], their best overall language gains occurred when SLT was received for up to 2 hours weekly [16.92 points (95% CI 3.80 to 30.04 points) on the WAB-AQ (37 IPD; 3 RCTs)]. Similarly, SLT for up to 2 hours weekly was also associated with the highest naming gains (measured on the BNT) for both groups [young: 17.35 points, 95% CI 8.32 to 26.38 points (10 IPD; 2 RCTs); old: 11.12 points, 95% CI 1.41 to 20.82 points (8 IPD; 2 RCTs)], although this finding was based on small IPD and data set numbers. Whereas the older group also made their highest functional communication gains [0.97 points (95% CI 0.38 to 1.57 points) on the AAT-SSC (41 IPD; 4 RCT)] in the context of receiving SLT for up to 2 hours weekly, younger participants' greatest functional communication gains were associated with 3–4 hours of SLT weekly [0.87 points (95% CI 0.53 to 1.22 points) on the AAT-SSC (74 IPD; 5 RCTs)] (see *Appendix 30, Table 34*, and *Appendix 34, Table 38*).

### Age and speech and language therapy dosage

In the context of a total SLT dosage of 20–50 hours, both younger and older age groups made their highest gains on overall language ability (as measured on the WAB-AQ) [young: 23.38 points, 95% CI 13.47 to 33.28 points (15 IPD; 3 RCTs); old: 15.95 points, 95% CI 5.08 to 26.83 points (16 IPD; 4 RCTs)], auditory comprehension (as measured on the TT-AAT) [young: 6.06 points, 95% CI 1.75 to 10.36 points (59 IPD; 6 RCTs); old: 5.80 points, 95% CI 1.35 to 10.24 points (34 IPD; 7 RCTs)] and naming (as measured on the BNT) [young: 13.56 points, 95% CI 5.30 to 21.79 points (57 IPD; 5 RCTs); old: 8.32 points, 95% CI 0.55 to 16.08 points (24 IPD; 5 RCTs)] (see *Appendix 30, Table 34*, and *Appendix 34, Table 38*). Similarly, the older group's highest functional communication gains (as measured on the AAT-SSC) were also associated with the same dosage of 20–50 SLT hours [0.86 points, 95% CI 0.36 to 1.36 points (31 IPD; 9 RCTs)], whereas the younger group's gains were best when SLT lasted 14–20 hours [1.12 points, 95% CI 0.47 to 1.78 points (6 IPD; 3 RCTs)] (see *Appendix 32, Table 34*, and *Appendix 34, Table 38*).

**Time since aphasia onset**

Participants for whom it was  $\leq 3$  months since their aphasia onset (early group: 324 IPD) showed higher change scores across all domains than participants for whom it was  $> 3$  months after stroke (late group: 158 IPD), potentially reflecting spontaneous recovery alongside SLT intervention benefits. Relative variance was modest ( $< 50\%$ ) across comparisons (see *Appendix 30, Table 34*, and *Appendix 34, Table 39*).

**Time since onset and speech and language therapy frequency**

The highest gains for the early group on overall language [27.75 points (95% CI 3.56 to 51.93 points) on the WAB-AQ (3 IPD; 1 RCT)] were seen alongside SLT 3 days per week, but this was based on few participants and one dataset. The next highest gain for the early group [21.42 points (95% CI 13.45 to 29.39 points); 150 IPD; 5 RCTs] occurred alongside SLT that was delivered 5 days weekly, which was when the late group's highest gains were also observed [6.32 points (95% CI 1.58 to 11.07 points); 44 IPD; 1 RCT]. The early group's best functional communication gains [1.55 points (95% CI 0.59 to 2.52 points) on the AAT-SSC (80 IPD; 1 RCT)] were seen when SLT was delivered three or four times weekly. The late group made no significant gains on functional communication (see *Appendix 30, Table 34*, and *Appendix 34, Table 39*).

The highest naming gains (measured on the BNT) for the early group [16.96 points, 95% CI 7.68 to 26.24 points (33 IPD; 3 RCTs)] were associated with SLT twice weekly, whereas the late group made their only significant gain alongside SLT 3 days weekly [2.81 points, 95% CI 0.60 to 5.02 points (78 IPD; 3 RCTs)]. The late group's best auditory comprehension gains were associated with SLT 4 or 5 days weekly [3.71 points (95% CI 1.41 to 6.00 points) on the TT-AAT (89 IPD; 5 RCTs)], and we found no evidence of significant auditory comprehension gains for the early group in this analysis (see *Appendix 30, Table 34*, and *Appendix 34, Table 39*).

**Time since onset and speech and language therapy duration**

There was no clear pattern in relation to SLT duration and best language gains by time since stroke. The early group made the best overall language ability gains [24.73 points (95% CI 12.53 to 36.92 points) on the WAB-AQ (26 IPD; 3 RCTs)] when SLT lasted  $> 4$ –10 weeks, best functional communication gains [1.16 points (95% CI 0.56 to 1.77 points) on the AAT-SSC (40 IPD; 3 RCTs)] when SLT lasted at least 10–20 weeks and best naming gains [12.50 points (95% CI 0.39 to 24.61 points) on the BNT (86 IPD; 3 RCTs)] in the context of  $> 20$  weeks of SLT. Relative variance for auditory comprehension analysis and the early group was unacceptably high, at  $> 50\%$  (see *Appendix 30, Table 34*, and *Appendix 34, Table 39*).

The late group's best overall language ability [9.30 points (95% CI 3.12 to 15.48 points) on the WAB-AQ (14 IPD; 1 RCT)] and auditory comprehension gains [5.20 points (95% CI 2.52 to 7.88 points) on the TT-AAT (49 IPD; 1 RCT)] were both associated with  $> 20$  weeks of SLT. The late group's best (and only significant) naming gains occurred with  $> 10$ –20 weeks of SLT [4.12 points (95% CI 1.79 to 6.45 points) on the BNT (33 IPD; 2 RCTs)]. Significant gains for the late group's functional communication were not evident in this analysis.

**Time since onset and speech and language therapy intensity**

The early group's highest overall language ability [24.27 points (95% CI 13.37 to 35.18 points) on the WAB-AQ (62 IPD; 2 RCTs)], naming [the only significant gain noted was 17.66 points (95% CI 3.95 to 31.36 points) on the BNT (10 IPD; 1 RCT)] and functional communication gains [1.29 points (95% CI 0.64 to 1.95 points) on the AAT-SSC (57 IPD; 2 RCTs)] were associated with receiving SLT for up to 2 or 3 hours weekly. The late group made their best overall language [6.25 points (95% CI 2.19 to 10.32 points) on the WAB-AQ (25 IPD; 2 RCTs)] and naming gains [5.58 points (95% CI 3.56 to 7.60 points) on the BNT (27 IPD; 2 RCTs)] alongside 3–4 hours of SLT weekly. In contrast, both early and late groups' only auditory comprehension gains (measured on the TT-AAT) occurred in the context of  $> 9$  hours of SLT weekly [early: 9.26 points, 95% CI 2.04 to 16.47 points (20 IPD; 2 RCT); late: 4.60 points, 95% CI 2.43 to 6.77 points (121 IPD; 4 RCTs)] (see *Appendix 30, Table 34*, and *Appendix 34, Table 39*).

### Time since onset and speech and language therapy dosage

Early-group participants achieved their greatest overall language [27.52 points (95% CI 18.32 to 36.71 points) on the WAB-AQ (27 IPD; 3 RCTs)], naming [20.67 points (95% CI 2.87 to 38.47 points) on the BNT (31 IPD; 2 RCTs)] and functional communication gains [1.25 points (95% CI 0.69 to 1.81 points) on the AAT-SSC (31 IPD; 3 RCTs)] in the context of between 20 and 50 hours of SLT. The late group also achieved their best (and only) significant naming gain alongside 20–50 hours of SLT [3.02 points (95% CI 0.90 to 5.15 points) on the BNT (50 IPD; 4 RCTs)], but, in contrast to the early group, their highest overall language [10.11 points (95% CI 4.22 to 16.0 points) on the WAB-AQ (15 IPD; 1 RCT)] and auditory comprehension gains [4.17 points (95% CI 1.68 to 6.66 points) on the TT-AAT (76 IPD; 3 RCT)] were associated with  $\geq 50$  and  $\geq 14$  hours of SLT in total. No significant gains from baseline were observed on measures of functional communication for the late group (see *Appendix 30, Table 34*, and *Appendix 34, Table 39*).

### Aphasia severity

Based on their language abilities at baseline, participants were dichotomised into mild–moderate (253 IPD) and moderate–severe aphasia groups (280 IPD). For each domain, median transformed language scores on the anchor measures, together with all available IPD in the RELEASE study database, supported the creation of two aphasia severity groups (see *Appendix 34, Table 40*). Across all domains, participants with moderate–severe aphasia achieved higher gains from baseline than those with mild–moderate aphasia. It is possible that the mild–moderate group's recovery on the anchor measures may have been masked by the assessments' ceiling effects, whereas the moderate–severe group had more scope to improve (see *Appendix 30, Table 34*, and *Appendix 34, Table 40*).

### Severity and speech and language therapy frequency

The moderate–severe group's highest overall language [18.25 points (95% CI 8.04 to 28.46 points) on the WAB-AQ (38 IPD; 5 RCTs)] and auditory comprehension gains [8.48 points (95% CI 3.67 to 13.28 points) on the TT-AAT (80 IPD; 5 RCTs)] were associated with receiving SLT 3 to 4 days weekly. The moderate–severe group's best naming gains were associated with receiving SLT up to twice weekly [13.07 points (95% CI 6.99 to 19.14 points) on the BNT (36 IPD; 4 RCTs)], and their best functional communication gains were associated with receiving SLT 4 days weekly [1.00 points (95% CI 0.48 to 1.51 points) on the AAT-SSC (55 IPD; 2 RCTs)].

The analysis found for the mild–moderate group, but their best gains for overall language and functional communication occurred when SLT occurred over at least 5 days weekly [9.85 points (95% CI 4.37 to 15.33 points) on the WAB-AQ (16 IPD; 2 RCTs)] and [0.66 points (95% CI 0.36 to 0.96) on the AAT-SSC (55 IPD; 8 RCTs)], respectively. Their best gains for naming [11.11 points (95% CI 5.61 to 16.60 points) on the BNT (11 IPD; 3 RCTs)] occurred when SLT took place 5 days weekly. These findings were based on small IPD numbers and data sets and should be interpreted with caution. Relative variance was unacceptably high ( $> 50\%$ ) for the analysis relating to the mild–moderate group's auditory comprehension (see *Appendix 30, Table 34*, and *Appendix 34, Table 40*).

### Severity and speech and language therapy duration

The moderate–severe group's best language gains on measures of overall language ability [23.53 points (95% CI 12.09 to 34.96 points) on the WAB-AQ (18 IPD; 2 RCTs)], functional communication [1.14 points (95% CI 0.78 to 1.49 points) on the AAT SSC (61 IPD; 4 RCTs)] and auditory comprehension [10.61 points (95% CI 3.91 to 17.30 points) on the TT-AAT (105 IPD; 3 RCTs)] were associated with SLT lasting  $> 20$  weeks. Few significant changes were observed among the mild–moderate group, but their best overall language [10.01 points (95% CI 2.42 to 17.60 points) on the WAB-AQ (16 IPD; 2 RCTs)] and naming gains [16.01 points (95% CI 6.60 to 25.41 points) on the BNT (26 IPD; 2 RCTs)] were also seen alongside SLT that lasted in excess of 20 weeks. For the moderate–severe group, the highest naming gains were associated with  $> 10$ –20 weeks of SLT [7.52 points (95% CI 1.08 to 13.97 points) on the BNT (71 IPD; 4 RCTs)]. Relative variance for auditory comprehension analysis and the mild–moderate group was unacceptably high, at  $> 50\%$  (see *Appendix 30, Table 34*, and *Appendix 34, Table 40*).

### Severity and speech and language therapy intensity

The moderate–severe group achieved their highest auditory comprehension [9.07 points (95% CI 2.57 to 15.58 points) on the TT-AAT (9 IPD; 2 RCTs)] and naming gains [12.45 points (95% CI 4.25 to 20.64 points) on the BNT (16 IPD; 2 RCTs)] in the context of up to 2 hours of SLT weekly, but IPD and RCT numbers were very low. The greatest overall language ability [20.04 points (95% CI 10.14 to 29.94 points) on the WAB-AQ (64 IPD; 4 RCTs)] and functional communication gains [0.98 points (95% CI 0.40 to 1.55 points) on the AAT-SSC (20 IPD; 4 RCTs)] for the moderate–severe group were associated with  $\leq 2$  and up to 3 SLT hours weekly and (on some measures) in excess of 9 hours weekly. For the mild–moderate group, the best gains on overall language ability [7.97 points (95% CI 3.37 to 12.57 points) on the WAB-AQ (48 IPD; 3 RCTs)] and naming [9.45 points (95% CI 4.64 to 14.26 points) on the BNT (19 IPD; 4 RCTs)] occurred in the context of  $> 9$  hours of SLT weekly with similar gains at other SLT intensities. Similarly, functional communication gains for the mild–moderate group were highest when SLT was  $> 4$  and up to 9 hours weekly [0.63 points (95% CI 0.26 to 1.01) on the AAT-SSC (27 IPD, 4 RCTs)]. Relative variance was unacceptably high ( $> 50\%$ ) for the mild–moderate group’s auditory comprehension analysis (see *Appendix 30, Table 34*, and *Appendix 34, Table 40*).

### Severity and dosage

Both severity groups made their greatest gains on overall language ability (as measured on the WAB-AQ) with at least 20–50 hours of SLT [moderate–severe group: 23.49 points, 95% CI 13.50 to 33.48 points (23 IPD; 3 RCTs); mild–moderate group: 8.73 points, 95% CI 1.95 to 15.51 points (8 IPD; 2 RCTs)]. The moderate–severe group’s highest auditory comprehension and functional communication gains were associated with  $> 50$  hours of SLT [8.89 points (95% CI 4.49 to 13.30 points) on the TT-AAT (142 IPD; 6 RCTs)], and [1.07 points (95% CI 0.78 to 1.37 points)] on the AAT-SSC (72 IPD; 6 RCTs)]. The mild–moderate group’s highest naming gains were associated with a SLT dosage in excess of 100 hours [12.96 points (95% CI 8.51 to 17.41 points) on the BNT (11 IPD; 3 RCTs)]. Relative variance was unacceptably high ( $> 50\%$ ) for naming gains (moderate–severe group) and auditory comprehension (mild–moderate group) analysis (see *Appendix 30, Table 34*, and *Appendix 34, Table 40*).

### Sex

Generally, female participants (211 IPD) had higher language gains across all domains than male participants (329 IPD), although these differences declined with increasing age ( $> 66$  years for naming and  $> 75$  years for functional communication). Interestingly, the best overall language gains for the oldest females [ $> 75$  years: 16.6 points (95% CI 8.38 to 24.89 points) on the WAB-AQ (68 IPD; 6 RCTs)] were similar to those of the youngest females [ $\leq 55$  years: 16.3 points, 95% CI 8.84 to 23.72 points (55 IPD; 10 RCTs)] (see *Appendix 30, Table 34*, and *Appendix 34, Table 38*). Relative variance was modest ( $< 50\%$ ) (see *Appendix 30, Table 34*, and *Appendix 34, Table 41*).

### Sex and speech and language therapy frequency

Male participants’ best overall language [13.59 points (95% CI 4.3 to 22.88 points) on the WAB-AQ (21 IPD; 2 RCTs)] and functional language gains [0.81 points (95% CI 0.09 to 1.53 points) on the AAT-SSC (6 IPD; 3 RCTs)] were associated with receiving SLT at least 5 or more days weekly. In contrast, females’ highest overall language gains [24.22 points (95% CI 7.73 to 40.71 points) on the WAB-AQ (5 IPD; 2 RCTs)] occurred alongside receiving SLT 3 days weekly, whereas their best functional language [1.01 points (95% CI 0.21 to 1.81 points) on the AAT-SSC (49 IPD; 3 RCTs)] and auditory comprehension gains [8.13 points (95% CI 2.65 to 13.60 points) on the TT-AAT (52 IPD; 5 RCTs)] were associated with receiving SLT 4 days weekly. The males’ best auditory comprehension gains [5.06 points (95% CI 1.41 to 8.71 points) on the TT-AAT (99 IPD; 8 RCTs)] also occurred alongside receiving SLT 4 or 5 days weekly. For both groups, their highest naming gains (on the BNT) also occurred when SLT was received up to twice weekly [females: 17.05 points, 95% CI 9.47 to 24.64 points (17 IPD; 4 RCT); males: 10.58 points, 95% CI 4.29 to 16.86 points (25 IPD; 4 RCTs)] (see *Appendix 30, Table 34*, and *Appendix 34, Table 41*).

### Sex and speech and language therapy duration

Male participants' best gains on overall language ability [16.72 points (95% CI 7.79 to 25.65 points) on the WAB-AQ (26 IPD; 3 RCTs)], naming [11.03 points (95% CI 5.38 to 16.67 points) on the BNT (51 IPD; 4 RCT)] and functional communication [0.67 points (95% CI 0.40 to 0.95 points) on the AAT-SSC (46 IPD; 4 RCT)] were all associated with > 10–20 weeks of SLT. Relative variance was unacceptably high for auditory comprehension (> 50%).

In contrast, female participants made their highest overall language [24.52 points (95% CI 13.22 to 35.81 points) on the WAB-AQ (12 IPD; 2 RCTs)] and auditory comprehension gains [6.97 points (95% CI 0.83 to 13.11 points) on the TT-AAT (63 IPD; 3 RCTs)] with > 20 weeks of SLT. Their functional communication gains were best alongside between 4 and > 20 weeks of SLT [0.97 points (95% CI 0.09 to 1.84 points) on the AAT-SSC (16 IPD; 2 RCTs)]. Relative variance was unacceptably high (> 50%) for auditory comprehension (male group) and naming (female group) (see *Appendix 30, Table 34*, and *Appendix 34, Table 41*).

### Sex and speech and language therapy intensity

For the female group, SLT for up to 2 hours weekly was associated with the highest gains on overall language ability [18.53 points (95% CI 7.46 to 29.59 points) on the WAB-AQ (37 IPD; 3 RCTs)], auditory comprehension [7.91 points (95% CI 1.82 to 14.00 points) on the TT-AAT (10 IPD; 2 RCTs) based on small numbers] and functional communication [1.15 points (95% CI 0.47 to 1.87 points) on the AAT-SSC (39 IPD; 4 RCTs)]. Their best naming gains occurred in the context of  $\leq 2$  to 3 hours of SLT weekly [13.48 points (95% CI 4.67 to 22.30 points) on the BNT (38 IPD; 5 RCT)].

In contrast, the male group's highest gains on overall language [15.13 points (95% CI 7.92 to 22.34 points) on the WAB-AQ (61 IPD; 3 RCTs)] and auditory comprehension [7.63 points (95% CI 3.77 to 11.48 points) on the TT-AAT (91 IPD; 6 RCTs)] were associated with > 9 hours of SLT weekly. Male participants' best functional communication [0.65 points (95% CI 0.40 to 0.89 points) on the AAT-SSC (97 IPD; 5 RCTs)] and naming gains [15.54 points (95% CI 6.94 to 24.14 points) on the BNT (10 IPD; 2 RCT)] were observed alongside between 2 and > 9 hours of SLT and up to 2 hours SLT weekly, respectively (see *Appendix 30, Table 34*, and *Appendix 34, Table 41*).

### Sex and speech and language therapy dosage

For both female and male participants, the best gains on overall language ability (measured on the WAB-AQ) were associated with at least 20–50 hours of SLT [females: 24.37 points, 95% CI 12.22 to 36.52 points (13 IPD; 2 RCTs); males: 15.61 points, 95% CI 6.23 to 25.00 points (18 IPD; 4 RCTs)], although IPD and RCT numbers were low.

Functional communication gains (measured on the AAT-SSC) were best for the male group alongside > 50 hours of SLT [0.70 points, 95% CI 0.48 to 0.91 points (93 IPD; 6 RCT)], whereas the female group's best gains occurred with 14–20 hours of SLT [1.59 points, 95% CI 0.57 to 2.61 points (4 IPD; 2 RCTs)], but this was based on very low IPD and RCT numbers. The next highest gain on functional communication for the female group was in the context of 20–50 hours of SLT [0.90 points (95% CI 0.38 to 1.42 points) on the AAT-SSC (43 IPD; 8 RCTs)]. Relative variance for both groups on the naming analysis was unacceptably high (> 50%) (see *Appendix 30, Table 34*, and *Appendix 34, Table 41*).

## Summary

Optimal language gains for younger and older participants were generally associated with similar levels of SLT frequency and dosage. Younger participants' best overall language and auditory comprehension gains were associated with high-intensity SLT (> 9 hours weekly). Although older participants' best auditory comprehension gains were also associated with high-intensity SLT, their highest overall language, naming and functional communication gains were associated with lower-intensity SLT ( $\leq 2$  hours weekly).

Generally, when differences were noted, participants in the early stages of aphasia recovery made their best overall language gains in the context of SLT that was less intensive and at a lower dosage than participants with long-standing aphasia (late group), who made their greatest gains alongside SLT that was at a slightly higher intensity and dosage.

The analysis of the mild-moderate group's language gains was limited by possible ceiling effects, although the group's best overall language and naming gains were associated with high intensity SLT (> 9 hours weekly). In contrast, the moderate-severe group's best gains on these measures were associated with less intensive SLT interventions (3-4 hours and up to 2 hours weekly, respectively).

Male participants' highest language gains were, when differences were observed, typically associated with SLT that was more frequent and intensive than the SLT regimens associated with the female participants' best language gains. The subgroup analyses were exploratory and, in some cases, based on small IPD and RCT numbers. The findings highlight some possible associations between specific participant subgroups' best language gains and SLT frequency, duration, intensity and dosage worthy of consideration in future research.

# Chapter 8 Confidence in cumulative evidence

## Overview

In this chapter, we consider the methodological quality of the RELEASE study, the meta-syntheses, risk of bias and confidence in the exploratory findings. Risk of bias at primary data set level (and IPD) is detailed in *Chapter 3*. We used the ROBIS tool to support our reflections on (1) the methodological steps taken to reduce the risk of meta-bias and (2) whether or not meta-biases may have affected the data synthesis and findings. We describe the results of investigations into heterogeneity, inconsistency and missing data, and present the findings from the prespecified sensitivity analyses.

## Methodological quality of the primary research data sets

Across the meta-syntheses, we prioritised IPD derived from RCT data sets, followed by re-analysis using the full data set inclusive of non-RCT IPD. Risk of selection bias was moderate in the RCTs informing our IPD network meta-analysis across language domains (see *Appendix 10, Figure 28*), with between 50% and 75% reporting adequate randomisation. Primary research study participant groups were comparable at baseline; only three data sets had participant groups that differed by age, sex or time since stroke. Risk of detection bias was low.

Three-quarters (75%) of RCT data sets included in the network meta-analyses across language domains reported outcome assessor blinding. Attrition bias was low (see *Appendix 10, Figure 28*). Many data sets retained participants to the end of the study, whereas others reported dropouts and non-adherence. Risk of reporting bias was highlighted, with some public domain IPD available at baseline only or partial contribution of some electronic data sets. However, these partial RCT data sets often lacked follow-up or intervention data, and thus were excluded from the network meta-analyses. By contrast, full IPD RCT data sets were also extracted from the public domain and some electronic data set contributions included IPD unreported in associated publications. Thus, the IPD RCT data sets informing the network meta-analyses were considered to be at a moderate to low risk of selection bias.

## Meta-synthesis and risk of bias

Supported by the ROBIS tool, we considered the extent to which the meta-analyses and network meta-analyses were at risk of bias.<sup>105</sup>

### *Specification of study eligibility criteria; selection bias*

The systematic review yielded a large number of records, which we screened for eligibility (see *Chapters 2 and 3*). Research teams were invited to contribute and collaborate. We had had no prior collaboration with 55 data set contributors. The systematic, inclusive approach to recruitment supported data set contributions that may not otherwise have been volunteered. We identified and extracted IPD from the public domain and grey literature in a range of languages (including 183 IPD from four RCTs, and 1988 IPD from 96 non-RCTs). These methodological steps were important in reducing the risk of selection bias in the meta-analyses.

The systematic development of the RELEASE study database used a priori eligibility criteria; reflected the scope of the research questions; and incorporated participant, study design and outcome data and IPD availability. Some research questions required SLT intervention data (see *Chapters 6 and 7*). Non-intervention data sets were also important, contributing to the exploration of patterns and

predictors of language recovery (see *Chapters 4 and 5*). The database eligibility criteria were deliberately inclusive and were adhered to throughout.

We accepted diagnosis of participants' aphasia in the primary research, confirming that it followed stroke. Aphasia associated with other neurological aetiologies was excluded. Formal approaches to aphasia diagnosis rely on validated language assessments, data required for inclusion in the study database and which informed our analysis. Data collection that was not quantitative or based on informal measures of language, were excluded as they were irrelevant to the research questions and analysis plan. We had no exclusions by study date, language of data collection or source, which might have affected electronic database searching or the contribution of unpublished clinical data sets. We made no other exclusions.

### ***Data set identification and selection; availability bias***

We made substantial efforts to identify all eligible IPD data sets, employing a broad search strategy (see *Appendix 1*) across databases and grey literature, and systematically inviting contributions from identified (potentially eligible) records and members of the Collaboration of Aphasia Trialists (see *Chapter 3*). The RELEASE study database also reflects data sharing with large independent aphasia databases [e.g. AphasiaBank, the Cantonese Aphasia Bank, Predicting Language Outcome and Recovery After Stroke (PLORAS)<sup>119</sup>] and clinical registries.

The RCT-optimised systematic search applied no restrictions to date, language or publications. We independently screened titles and abstracts, followed by double-checking to minimise any errors in the selection of eligible texts. We listed the data sets identified as potentially eligible for inclusion but for which the IPD were unavailable, which suggests additional RCTs (46 inclusive of a standard care or experimental SLT intervention) may exist (see *Report Supplementary Material 2*). We were unable to confirm that these data sets (and associated IPD) typically described as aggregate data in full text reports met our eligibility criteria or that the IPD remained available. Confirmation of the eligibility of included datasets was only possible following communication with the primary researchers and careful review of the IPD (see *Chapter 3*). Yet, it is probable that some eligible IPD existed but were unavailable to our analysis.

From a research-waste perspective, the possible existence of eligible but unavailable data is disappointing given that several of the planned analyses were not possible or unstable owing to lack of data availability (see *Chapters 4–7*). Additional data would have strengthened the network meta-analyses, potentially providing more links between network nodes (see *Chapters 6 and 7*) and greater insights. The number of included data sets, however, was sufficient to address the main RELEASE research questions.

The RELEASE study data set was predominantly based on data from English-speaking, high-income countries with well-developed SLT and stroke services. Non-English-language aphasia assessment tools are lacking, and limited (or absent) SLT services are important constraints on data-gathering in some countries. Thus, it is unlikely that we omitted many large, robust language data sets from non-English speaking countries.

### ***Data collection and study appraisal (ROBIS domain 3)***

We sought to minimise data extraction and synthesis errors. Data extraction was rigorously checked by a second reviewer. Data extraction of the complex SLT intervention descriptions was independently conducted by two researchers and was reviewed by the primary researchers. Collaborators informed the categorisation of narrative descriptions of SLT interventions by (i) target of impairment and (ii) a theoretical approach that supported data synthesis and analysis. We provided an opportunity to examine the data sets that informed the analyses, presenting aggregate data set descriptions (see *Chapter 3*) and individual data set overviews (see *Report Supplementary Material 1*). We detailed the approach to data synthesis, data item descriptions and group labels used in the analysis (see *Chapter 3*). Formal approaches to risk-of-bias analysis at primary data set level were described and undertaken by an independent reviewer, with a second reviewer rigorously checking that analysis (see *Chapter 3*).

## Synthesis and findings

### Data restrictions

We experienced restrictions in retrieving potentially eligible IPD data sets (described above) and limitations in accessing the full IPD data sets for some electronically contributed and public domain data sets. Other unavailable data included data sets that used a comprehensive aphasia assessment battery (comprising several subtests), but only summary test scores were recorded and reported. We experienced no other restrictions on data availability.

### Bias

We found no evidence of publication bias based on study size (see *Appendix 32*), although publications with an earlier date had a higher proportion of non-significant results than findings reported in later publications ( $p = 0.014$ ). We sought to reduce the risk of researcher bias by assigning data sets numerical IDs, so that collaboration-wide consensus decisions could be reached based on anonymised data sets, rather than the primary research teams.

### Data synthesis

The primary data sets focused on language recovery and people with aphasia. Some included a SLT intervention; these were included in the network meta-analyses. Clinically, individual data sets were very similar in population, intervention, comparators and outcomes (see *Report Supplementary Material 1*), but this was not formally tested.

We used a random-effects model. Application of the Wu–Hausman<sup>108</sup> test for fixed- versus random-effects model (described below) indicated that there was no difference based on these two models of analysis (see *Appendix 33, Table 37*). We considered heterogeneity by measuring relative variance. Any analysis that breached the prespecified threshold of acceptable variance (> 50%) was omitted from the interpretation of the data.

The one-stage IPD network meta-analyses did not incorporate aggregate summary data. We prioritised IPD derived from RCTs, but also considered the findings inclusive of IPD from non-RCTs, which were typically in keeping with the RCT IPD findings. Analysis on a single data set was not conducted. The prespecified minimum data analysis sample of two data sets (minimum of 20 IPD) was adhered to. However, the analysis occasionally generated clusters of small IPD or data set numbers; in such cases, these were treated with caution.

When IPD availability allowed, we conducted a prespecified subgroup analysis (see *Chapter 7*) to explore the possibility of heterogeneity between clinically relevant participant subpopulations. Based on the preparatory exploration of the data set, we included one post hoc subgroup. Alternative approaches to the data synthesis are unlikely to alter the findings.

## Quality of the evidence

We considered the degree to which we could be confident of the study findings, based on the quality of the evidence. The patterns of language recovery findings lacked data for several planned analyses, and these were ungraded (*Table 11, part A*). The distribution of language scores at baseline was based on large numbers of IPD and it is unlikely that additional research will affect the finding. We have assigned a GRADE rating of 'high' (see *Table 11, part A*).

TABLE 11 Summary of findings

Absolute proportion change scores	Overall language ability (WAB-AQ) (0–100)	Auditory comprehension (TT-AAT) (0–50)	Naming (BNT) (0–60)	Other spoken language (PICA) (0–16)	Reading comprehension (CAT reading) (0–74)	Writing (CAT writing) (0–76)	Functional communication (observer-rated) (AAT-SSC) (0–5)	Quality of the evidence (GRADE)
<b>(A) Pattern of language recovery</b>								
Natural history: insufficient data								-
No SLT (historical SLT) vs. SLT-treated participants: insufficient follow-up data								-
As time to study enrolment increased, the proportion of change from baseline seen all across domains decreased								High
Median (IQR) (%)	8.4 (1.3–22)	8.0 (0–18)	3.9 (0.3–21.7)	3.1 (0–8.1)	-	1.3 (-1.6–8.6)	10 (0–26.6)	Moderate <sup>a</sup>
IPD (RCTs) (n)	418 (11)	508 (17)	346 (14)	155 (2)	-	41 (3)	608 (16)	
<b>(B) Predictors of language recovery: severity, age, time since stroke and sex</b>								
Multivariable	<ul style="list-style-type: none"> <li>Severity: <math>p &lt; 0.0001</math></li> <li>Sex: <math>p = 0.018</math></li> </ul>	<ul style="list-style-type: none"> <li>Severity: <math>p &lt; 0.0001</math></li> <li>Age: <math>p = 0.003</math></li> </ul>	Severity: $p = 0.0052$	<ul style="list-style-type: none"> <li>Age: <math>p = 0.02</math></li> <li>Time: <math>p = 0.01</math></li> </ul>	<ul style="list-style-type: none"> <li>Severity: <math>p = 0.0004</math></li> <li>Age: <math>p = 0.0094</math></li> </ul>	Time: $p = 0.027$	<ul style="list-style-type: none"> <li>Severity: <math>p &lt; 0.0001</math></li> <li>Age: <math>p = 0.038</math></li> <li>Sex: <math>p = 0.021</math></li> </ul>	Moderate <sup>a</sup>
IPD	482	550	385	231	88	47	544	
p-value, points (95% CI)	<ul style="list-style-type: none"> <li>Age: <math>p = 0.02</math>, 1.02 (1.00 to 1.04)</li> <li>Time: <math>p &lt; 0.002</math>, 0.99 (0.98 to 0.99)</li> </ul>	<ul style="list-style-type: none"> <li>Time: <math>p = 0.003</math>, 0.99 (0.99 to 1.00)</li> </ul>	Time: $p = 0.002$ , 0.99 (0.98 to 0.99)	Time: $p = 0.0001$ , 0.87 (0.80 to 0.93)	-	Time: $p = 0.0002$ , 0.90 (0.86 to 0.95)	Time: $p < 0.0001$ , 0.98 (0.98 to 0.99)	<ul style="list-style-type: none"> <li>Moderate<sup>a</sup> for overall language ability, auditory comprehension, naming</li> <li>Low<sup>b</sup> for reading, writing and other spoken language</li> </ul>
IPD (RCTs) (n)	418 (11)	508 (17)	346 (14)	155 (2)	-	41 (3)	608 (16)	

Absolute proportion change scores	Overall language ability (WAB-AQ) (0–100)	Auditory comprehension (TT-AAT) (0–50)	Naming (BNT) (0–60)	Other spoken language (PICA) (0–16)	Reading comprehension (CAT reading) (0–74)	Writing (CAT writing) (0–76)	Functional communication (observer-rated) (AAT-SSC) (0–5)	Quality of the evidence (GRADE)
<b>(C) SLT and peak rehabilitation gains by language domain</b>								
<i>Parameter (95% CI)</i>							<i>Functional communication (AAT-SSC) (0–5)</i>	
Frequency of SLT	14.95 (8.7 to 21.2)	5.86 (1.6 to 10.0)	12.05 (6.5 to 17.6)	–	–	–	0.78 (0.48 to 1.1)	<ul style="list-style-type: none"> <li>Moderate<sup>a</sup> for overall language ability, auditory comprehension and functional communication</li> <li>Low<sup>b</sup> for naming</li> </ul>
	SLT > 4 to 5 days weekly	SLT > 3 to 4 days weekly	SLT up to 2 days weekly	–	–	–	SLT > 4 to 5 days weekly	
	IPD 194 (6 RCTs)	IPD 114 (5 RCTs)	IPD 42 (3 RCTs)	–	–	–	IPD 155 (8 RCTs)	
Duration of SLT	17.27 (9.7 to 24.8)	6.79 (1.7 to 11.9)	8.38 (1.2 to 15.5)	–	–	–	0.8 (0.3 to 1.3)	<ul style="list-style-type: none"> <li>Low<sup>b</sup> for naming and duration<sup>c</sup></li> </ul>
	> 10–20 weeks of SLT	> 10–20 weeks of SLT	> 20 weeks of SLT	–	–	–	≥ 4 to 10 weeks of SLT	
	IPD 45 (3 RCTs)	IPD 93 (5 RCTs)	IPD 134 (3 RCTs)	–	–	–	IPD 57 (2 RCTs)	
Intensity of SLT	15.9 (8.1 to 23.6)	7.3 (4.1 to 10.5)	13.2 (5.8 to 20.6)	–	–	–	0.77 (0.36 to 1.2)	<ul style="list-style-type: none"> <li>Moderate<sup>a</sup> for overall language ability, auditory comprehension and functional communication</li> <li>Low<sup>b</sup> for naming</li> </ul>
	SLT for up to 2 hours weekly	SLT for > 9 hours weekly	SLT for up to 2 hours weekly	–	–	–	SLT for up to 2 hours weekly	
	IPD 74 (3 RCTs)	IPD 141 (6 RCTs)	IPD 18 (2 RCTs)	–	–	–	IPD 83 (4 RCTs)	
Dosage of SLT	18.37 (10.6 to 26.2)	5.23 (1.5 to 9.0)	12.48 (1.3 to 23.6)	–	–	–	0.94 (0.3 to 1.6)	<ul style="list-style-type: none"> <li>Moderate<sup>a</sup> for overall language ability, auditory comprehension and functional communication</li> <li>Low<sup>b</sup> for naming</li> </ul>
	> 20 to < 50 hours of SLT	> 20 to < 50 hours of SLT	Up to 5 hours of SLT	–	–	–	> 14 to 20 hours of SLT	
	IPD 31 (4 RCTs)	IPD 90 (7 RCTs)	IPD 28 (2 RCTs)	–	–	–	IPD 11 (3 RCTs)	
–, insufficient data.								
a Downgraded one level from high to moderate as there were limitations identified in the availability of potentially relevant data sets and in the accessibility of post-intervention follow-up data for some IPD reported in the public domain.								
b Downgraded for insufficient data to inform the analysis.								
c There was little variation in response to different durations.								
<b>Note</b>								
GRADE level of confidence in data synthesis: high – additional research is very unlikely to change our confidence in the findings; moderate – additional research is likely to have an important impact on our confidence in the findings and may change these findings; low – additional research is very likely to have an important impact on our confidence in the findings and is likely to change our findings.								

We graded the evidence informing the absolute proportion change scores, multivariable analysis and the predictors of recovery (based on RCT IPD) as moderate level of evidence (see *Table 11*, part A). This was downgraded from high in recognition of the number of potentially eligible data sets identified, but which were not included in the analysis. We graded reading, writing and other spoken-language findings as low because greater availability of data is likely to alter these findings (see *Table 11*, part B).

The network meta-analyses considering the optimum SLT intervention regimen by language domain was rated low for duration comparisons and naming outcomes, downgraded from moderate because of the lack of IPD and/or unstable network geometry (see *Table 11*, part C). Further research will contribute to the data, changing confidence in the findings. The overall language ability, auditory comprehension and functional communication findings relating to SLT frequency, intensity and dosage were rated as moderate because of the higher IPD numbers informing these network meta-analyses and more stable network geometry ( $\approx 500$  IPD; see *Appendices 11–14*) (see *Table 11*, part C). The subgroup network meta-analyses were based on even smaller IPD numbers, and were thus also graded as very low (see *Appendix 30*, *Table 34*).

### Heterogeneity

We noted more instances of high heterogeneity (identified as  $> 50\%$  relative variance) in the subgroup network meta-analysis, due, in part, to smaller IPD sample sizes and more instances of orphan interventions. These subgroup analyses were more exploratory than confirmatory. We chose to present all the results, highlighting instances of high heterogeneity ( $> 50\%$ ) in the relevant tables for information (see *Appendices 30* and *34*).

### Exploration for inconsistency

Owing to the scarcity of direct comparisons for most pairwise nodes in the network meta-analysis (see *Appendices 11–14* many contained a single study and were often based on a small number of IPD; see *Appendix 34*), a comparison of direct and indirect evidence was not useful. Direct comparisons within small, single RCTs would be likely to have large CIs that would be difficult to show a difference in, unless that difference was excessive. Instead, we examined inconsistency between studies by calculating the relative proportion of the variability (the difference between the predicted value and the actual value) that appeared to be solely due to differences between studies, and that of the null model (fitting only an intercept or constant term). A high proportion in this case would imply that most of the differences in the data were due to differences between studies, and thus imply that the studies were heterogeneous and thus too dissimilar for reliable meta-analysis.

### Missing data/missing completely at random

Contributed data sets tended to have either nearly complete or nearly incomplete data for the majority of variables, and so rarely exceeded the prespecified threshold of 20% missing data. Many variables of interest were insufficiently collected across the data sets to include in the analyses. Comparisons of missingness with the main demographic variables did not reveal any systematic relationships (i.e. not missing at random). Other variables were well represented and were sufficient across the database and by primary research data set to include in our analyses (e.g. stroke type), but there was a lack of variability in subclassifications (e.g. some stroke types had only a few participants), making estimates for that variable imprecise, and, invariably, non-significant.

## Publication bias

We included both published and unpublished IPD (including three clinical registry data sets and a RCT) in the RELEASE study. Funnel plots were not possible because of the nature of the data set. Instead, we considered the distribution of studies based on the number of participants recruited and the publication of a significant finding. We found no evidence of publication bias by sample size ( $p = 0.77$ ; see *Appendix 32*).

## Other biases

The risk of potential carry-over within crossover data sets was addressed by extracting the data up to the point of crossing over, but not beyond. We extracted primary research details (see *Report Supplementary Material 1*) and, although some data sets did not share language recovery and rehabilitation as their main study objective, there was no indication that this had any impact on the data extracted for the RELEASE study.

## Sensitivity analyses

We conducted a series of pre-planned sensitivity analyses to examine decisions made in the data synthesis and the potential impact that these decisions may have had on the findings.

### Choice of language measurement

Some primary data sets had IPD on two or more assessment tools that were eligible contributors to data synthesis relating to a single language outcome. Inclusion of all relevant data was not possible as it would result in 'double-counting' participants in that outcome. We chose which language assessment would contribute to the data synthesis for that language domain (see *Report Supplementary Material 18*) using a structured, systematic approach to support decision-making:

- We reviewed the numbers of missing data (considering data at study entry and follow-up time points). The more complete data set (IPD) was prioritised.
- When there was equivocation (i.e. both assessments had equal IPD numbers, including at follow-up), we prioritised the inclusion of IPD collected on the anchor measure.

Most overlapping data situations were resolved using this approach. Only a few remained, involving a small number of IPD and data sets, and these decisions were unlikely to affect the study findings and conclusions. For example, one data set using the TOMs included data from both activity and participation subtests, available on equal numbers of IPD. We arbitrarily included the activity data, but conducted a sensitivity analysis by replacing the activity item with the participation data in the network analysis (see *Appendix 9, Tables 16–18*). There was no indication of a notable difference between the findings. Each case of overlapping data eligibility was recorded, along with the choices available and decisions reached (see *Report Supplementary Material 18*). The numbers of IPD and data sets were insufficient to support any formal sensitivity analysis or the production of any meaningful result.

### Exclusion of minority measures

We plotted the distribution of all transformed measures over time and by language domain, and observed that the spread of data points gathered on all language measures as profiled by each language domain overlapped (see *Appendix 6, Figure 27* and *Appendix 7, Table 14*). There did not appear to be a clustering of transformed language measures that were generated from any one contributing assessment. The transformed values generated by each of the language assessments were valid and within an expected range.

**Random or fixed effects**

We considered the impact of the choice of a random-effects model over a fixed-effects model, using both the Wu–Hausman and the alternative Wu–Hausman. We compared the difference between the estimates of the covariate and standard error of baseline score. We had inadequate data for the reading comprehension item (one RCT). For all other language domains, the W score was  $< 3.841$ . For the alternative W, most values were  $< -1.96$  or  $> 1.96$ , except for those based on functional communication ( $-1.9680$ ). We also noted a relative variability of 41.1% for the naming data set, although this dropped to 30% when other variables were included in the model (see *Appendix 33, Table 37*). We rejected the null hypothesis that fixed effects were more efficient.

**The inclusion of historic data sets**

We explored the availability of historic data sets and what bias there may be in the inclusion of data sets gathered in the 1970s, as treatment responses may reflect health-care interventions (SLT and stroke related) at that time. We found no evidence that date of recruitment contributed to the findings based on language outcomes (see *Appendix 31*).

**Excluding non-randomised controlled trial data sets**

Throughout the analysis relating to patterns of recovery, predictors of recovery and optimum approaches to SLT, we prioritised the data analysis on IPD from RCT data sets only, and then re-ran the analysis inclusive of IPD from non-RCT data sets. We observed only modest (non-significantly) higher values in the context of some analyses inclusive of non-RCT data set (often with wider CIs) (see *Chapters 4–6*). Inclusion of the non-RCT data sets augmented the IPD on language abilities of people with aphasia at a specified time point from onset and in analyses where RCT data were lacking or absent. The IPD derived from non-RCTs and RCTs contributed to the calculation of median aphasia severity and age at the baseline assessment for the prespecified subgroup analysis (see *Chapter 7*). However, given the challenges and risk of overstating subgroup analysis results, we restricted the subgroup analyses to RCT IPD only.

**Registry data sets and impact on findings**

The database included five registry data sets (853/5928 IPD; 14%) that provided valuable data on international, clinical populations with aphasia. Summary statistics on the registry population demographics indicated that the data sets were broadly similar to other non-RCT data sets in terms of age, sex, time since stroke, aphasia severity, handedness and years of education (see *Appendix 5, Table 13*). Registry data contributed to the analysis of patterns and predictors of recovery only (see *Chapter 4*). Reporting of therapy interventions in the registries was mostly absent or insufficient to support profiling of the intervention, and thus inclusion in that analysis.

**Summary**

The RELEASE study analysis was based on high- and moderate-quality data sets (see *Chapters 4–7*). Wherever possible, we sought to reduce the risk of selection and availability bias, and bias in the data collection, study appraisal and data synthesis processes. We found no indication of important clinical or significant statistical heterogeneity. Isolated cases of high relative variance were reported but not taken forward into the findings. We found no indication of publication or historical bias, or that any decisions taken during the meta-synthesis may have biased the findings.

# Chapter 9 Discussion and conclusions

## Overview

In this chapter, the exploratory findings relating to the patterns and predictors of language, optimal SLT interventions and potential tailoring of SLT for subgroups of people with aphasia after stroke are summarised. We then consider the strengths and limitations of these findings, before describing the study's patient and public involvement (PPI), the clinical and research implications, and the conclusions.

## Summary of findings

### *Patterns of language recovery*

We explored the patterns of language recovery among participants who had access to SLT (in the context of the primary research). We looked at when recovery occurred and in what language domain. We had insufficient data to consider whether or not the patterns of language recovery varied by different languages spoken.

Participants allocated to receive SLT demonstrated higher language scores over the study duration across all language domains, with modest gains observed on measures of other spoken language, reading comprehension and writing. Data for participants who had only historical SLT were limited, as many were permitted SLT access after the comparison group completed the SLT intervention period and prior to follow-up data collection points (see *Table 11*).

We had insufficient data from a pure natural history population (participants who, we could be reasonably confident, had no access to SLT after stroke) to plot language recovery by language domain. With the benefits of SLT for aphasia well established, it is ethically unlikely that such data will be available in the future, unless gathered in an international context in which SLT for aphasia is not part of usual care; however, in such contexts, other aspects of stroke care are also likely to differ.

When considering participant data at study entry time points only, time since stroke was inversely associated with the severity of language impairment across all language domains, suggesting spontaneous improvement or selection bias in data sets recruiting at later time points following stroke. Absolute proportion of change in participants' language abilities over time was greatest on measures of functional communication, overall language ability and auditory comprehension.

### *Predictors of recovery*

We explored the predictors of language recovery outcomes following aphasia by individual characteristics (age, education, cognition, monolingual or multilingual), rehabilitation environment (social support, socioeconomic demographics, ethnicity), stroke profile (severity, lesion type, size, location) and by language domain (overall language ability, auditory comprehension, spoken language, reading comprehension and writing). We were unable to take some analyses forward because of insufficient data (the role of monolingualism or multilingualism, ethnicity, cognition) or because the format of available data prevented meaningful synthesis (education, socioeconomic demographics). Lesion type and size are currently being investigated by a collaborating research group (e.g. PLORAS<sup>119</sup>); to avoid research waste, these were not taken forward in this study.

Across all language domains, when a significant change from baseline was evident, the greatest change in language performance from baseline was among participants enrolled within 1 month of stroke.

Change in language performance scores from baseline appeared to lessen with increasing time from stroke to study enrolment.

Using regression, we examined the proportion of recovery within each language domain and found that increasing time from stroke to study entry was significantly associated with poorer recovery on all language domains. Increasing age was significantly associated with poorer recovery on overall language ability. Sex was also included owing to its known relationship with other stroke outcomes (see *Table 7*). Each of these covariates contributed to base models in subsequent analyses (see *Table 11*).

### ***Optimum speech and language therapy interventions for aphasia after stroke***

Using a one-stage network meta-analysis with direct and indirect comparisons, we explored language recovery in the context of SLT aphasia rehabilitation intervention regimen (timing, frequency, duration, intensity, dosage, home-based therapy), approach (theoretical approach and impairment target) and delivery model (functional relevance, one to one or group).

Controlling for age, time since stroke and sex, we found that SLT frequency, duration, intensity and dosage were significantly and selectively associated with language outcomes. Auditory comprehension gains were associated with the frequency, intensity, dosage (including home practice) and tailoring of SLT. Naming gains were associated with the frequency and dosage of SLT. Functional communication gains were associated with dosage (see *Report Supplementary Materials 5–17*).

We considered language gains made from baseline, and found that SLT regimen was associated with language recovery and varied by domain. Overall language ability and functional communication scores improved most in the context of receiving SLT for up to 2 hours weekly, delivered daily (> 4–5 days weekly). Auditory comprehension gains were greatest alongside SLT in excess of 9 hours weekly, over 3–4 days. The best overall language gains were associated with 20–50 hours of SLT. The greatest overall language and functional communication gains were seen in the context of mixed SLT approaches, whereas SLT aimed at improving word-finding was associated with the greatest gains in auditory comprehension. Language recovery on these measures was greatest in the context of SLT tailored by functional relevance to the participant and when home practice was prescribed. We found no indication that the expertise of the SLT provider, the mode of therapy (face to face, group or computer-based), the context of SLT delivery or the theoretical approach were related to participants' language change from baseline, although naming, duration and the theoretical approach findings were based on a limited data set (see *Table 11*).

### ***Speech and language therapy interventions: age, time since stroke, severity and sex subgroups***

Subgroups were defined by individual (age, sex), stroke (time since onset) and aphasia characteristics (severity at baseline). The association between language scores and SLT intervention components was examined using a network meta-analysis approach. Participant numbers were low and the findings were treated with caution.

Language recovery was best for both younger and older participants in the context of 20–50 hours of SLT over several SLT days weekly. For both groups, auditory comprehension improved most when associated with highly intensive SLT (> 9 hours weekly). The best language gains for the older group on other domains occurred alongside less intensive approaches (up to 2 hours of SLT weekly).

When significant changes from baseline were observed, participants within 3 months of aphasia onset made most language gains in the context of 20–50 hours of SLT, delivered two to four times weekly for up to 2 hours each week. In contrast, participants starting SLT > 3 months after stroke made their best gains alongside SLT in excess of 50 hours in total, delivered four to five times weekly, for 3–4 hours weekly. The only variation to this profile was that, regardless of time since onset, both groups made their best gains in auditory comprehension with > 9 hours of SLT weekly.

Language gains from baseline were greater for participants with moderate–severe aphasia than for those with a milder aphasia across language domains. People with milder aphasia, already scoring highly on assessments, may have had less scope to demonstrate improvement on assessment tools unable to capture language change at or close to the highest possible score (the ceiling effect). The moderate–severe group’s best language gains were associated with frequent SLT (three to five times weekly), for between 2 and 4 hours weekly, and a total dosage of 14–50 hours, or more, depending on the language outcome.

Language gains across all domains were higher for females than for males. Females’ highest language gains occurred with up to 2 hours of SLT weekly, delivered over 2–4 days. Males’ highest language gains occurred with intensive, daily SLT (3–4, or even > 9, hours weekly, depending on language modality). Males’ and females’ best overall language gains were associated with 20–50 hours of SLT, although higher SLT dosage (> 50 hours) was associated with the highest auditory comprehension gains for female participants and the highest functional communication gains for male participants.

## Strengths

### *Diversity of data set*

This international collaboration of multidisciplinary researchers created one of the largest IPD data sets on 5928 people with aphasia and on language after stroke, gathered across 174 clinical or research settings, incorporating pre-existing databases, RCTs, non-RCT designs and clinical registries. The diversity of data sets, languages, severities and contexts (clinical and research) supports generalisation of the results. The primary research data sets met all the eligibility criteria and were further filtered for each research question. The database was sparse, with each data set typically including just some of the variables relevant to the analysis. Thus, the high number of data sets included in the database was essential to ensure sufficient overlap in the availability of variables to support the planned analysis. In addition, we required enough data sets to ensure an adequate sample size to explore the characteristic diversity of this population group, a wide range of language outcomes and the complexity of SLT interventions for aphasia.

### *Quality of data set*

The database included RCTs generally graded as being at a low risk of bias (random sequence generation, concealment of allocation, blinding and few with unexplained attrition). For non-RCT data sets, the lack of randomisation was a risk of bias. Blinding of outcome assessors and the comparability of the groups at baseline were reassuring. The analyses based on IPD derived from RCTs were typically similar to the analyses that included the non-RCT IPD data sets.

We included unpublished IPD and eligible data sets identified by the systematic review. Responses to invitations to contribute data sets and inclusion of extensive IPD from the public domain (including complete RCT data sets) contributed to a reduction in the risk of publication bias. The formal assessment of publication and historical bias found no evidence to suggest that the findings were influenced by such biases.

Data relevant to the analyses were carefully identified, extracted and subsequently checked by a second researcher and (when possible) the contributing primary researchers. Data were additionally checked by reviewing plots and distributions, network graphs and through constant reference to the primary research data set to ensure accuracy. We standardised language recovery outcome by language domain across data sets and categorisation of SLT interventions by impairment target and theoretical approach through consensus with collaborators.

### *Language data*

The language data reflect participants’ performance across several language modalities, gathered using specialised language measurement tools rather than a brief language item on a stroke scale.<sup>29</sup> Only published language measures were included. Screening tool data were excluded.<sup>97</sup> We preserved a

clinically relevant language measurement reference, transforming the data to a single anchor measure for each outcome. Thus, measures of language change could be interpreted in the context of a clinically relevant scale as used in aphasia rehabilitation. The international multilingual collaboration supported data extraction and analysis of non-English aphasia assessment tools.

### ***Speech and language therapy data***

Working across an international, multilingual context supported the SLT data extraction, analysis and interpretation. Classification of SLT approaches by treatment target and theoretical approach was undertaken by the collaboration, and, following consensus review and approval (with minor edits), was sustained throughout the project. The aphasia intervention classification framework is an important adjunct to the TIDieR checklist to encourage transparency of reporting in SLT intervention studies for aphasia after stroke.<sup>86</sup>

### ***Individual participant data one-stage approach to meta-analysis***

Findings from IPD and group summary meta-analysis can be equivalent, but the IPD data synthesis approach allowed inclusion of different data in existing meta-analyses. We included unpublished, clinical data sets, IPD, outcomes and extended follow-up time points excluded from aggregated published reports addressing some of the risks of outcome reporting bias. Using participants as the unit of analysis, we also had more power to identify clinically relevant interactions, which can be more easily interpreted to specific clinical populations than data derived from aggregate data alone. Study variability was monitored; only findings for which study variability was low to modest were reported, and these variations were highlighted to the reader. The multiple analyses were presented in a balanced manner, with all non-significant findings available for reference.

## **Limitations**

### ***Exploratory approach***

We adopted an exploratory approach to the analysis, and results should be interpreted in this context. The ambition was to inform prioritisation, design, delivery and reporting of definitive research to confirm (or refute) these findings. It was impossible to anticipate the completeness of the final database. Network diagrams accompanied each comparison by language domain and every effort was made to ensure well-constructed networks. When it was not possible to make comparisons between all interventions, this was reported as an unreliable analysis. There were few direct comparisons or, when available, comparison was limited to one or two data sets. Network graphs were reasonably balanced, but only because of the sparsity of direct comparisons between each node. The availability of data and the network geometry highlighted comparisons that were unavailable; these evidence gaps should be addressed as a priority in future RCTs.

### ***Diversity of data set***

This database demonstrated a marked imbalance towards English-language data (more than half the data set), with other languages often represented by a single data set. We applied no language restrictions to the searching or inclusion criteria. The imbalance in language representation is reflective of the wider aphasia research literature. Recovery from aphasia in monolingual and bilingual stroke survivors may differ. Languages vary from each other in grammatical structure (e.g. English grammar, compared with agglutinating languages such as Finnish) and writing systems (Latin alphabetic, e.g. English, vs. Greek alphabet or Chinese logographic scripts). Non-English aphasia research has historically been hampered by the lack of rigorous, valid and reliable aphasia assessments, although some co-ordinated initiatives are under way that aim to change this landscape.<sup>120</sup>

Reading comprehension and writing interventions and outcomes were also limited in their representation in the database, hindering the insight into impact on and recovery of these language domains.

### **Data collection limitations**

Demographic, language and SLT intervention data, although sufficient for the purposes of the primary research activities, were often limited in their contribution to the secondary data analyses. For example, the analysis was often limited by a lack of outcome data captured at both baseline and follow-up time points. Historical SLT groups were rarely measured following the comparator intervention period. Participants allocated to receive SLT in the primary research had limited post-intervention follow-up, thereby limiting our insight into long-term maintenance of language recovery gains.

We also undertook a comprehensive literature search and systematically invited contributions and included IPD from the public domain to ensure that the breadth of included data sets would compensate for the anticipated sparsity of the data. Data extraction of IPD in the public domain was, as expected, often limited to baseline data, but also included four complete RCT IPD data sets. It was not possible to include all datasets identified as potentially eligible. In many cases we had no response to our invitation, while in others the IPD was no longer available.

### **Descriptions of speech and language therapy interventions**

Speech and language therapy intervention descriptions typically lacked information on tailoring, adherence and home practice tasks. SLT intervention descriptions were rarely available at IPD level, and SLT intervention data were insufficient to support all the planned analyses, in some cases resulting in a network meta-analysis with too few connections to permit complete direct and indirect comparisons. For other networks, we used a reference group to close the analysis loop and strengthen the analysis, but some orphan groups were still evident (see *Appendices 11–14*). These networks gaps should be addressed in targeted RCT-based comparisons. Other SLT interventions are reported in the wider literature, but these were not represented in this database because of unavailability or issues with eligibility.

### **Language outcome limitations**

We sought to adopt the ICF framework in the RELEASE study to describe the impact of aphasia and rehabilitation interventions. Language impairment was well represented across several language domains. Measures of communication participation or activity items, however, were typically represented by isolated data sets and available data items could not be meaningfully synthesised. The development of new assessments that capture such constructs<sup>121</sup> and recent consensus on a core outcome set for aphasia research<sup>122</sup> are important steps to ensuring that future aphasia research will reflect outcomes of importance to people with aphasia, their families and health-care professionals.<sup>122</sup>

### **Stroke description limitations**

The description of stroke (and related health data) was limited in the included aphasia data sets. Stroke severity and acute care stroke interventions, such as thrombolysis, are important rehabilitation and recovery factors.<sup>29,123</sup> Comorbidities and stroke risk factors are relevant to aphasia recovery<sup>29</sup> and stroke rehabilitation.<sup>124</sup> Standardisation of data collection on these items across all stroke and aphasia recovery research would support further clarity on their relevance to aphasia recovery.<sup>125,126</sup>

### **Inclusion limitations**

The planned analysis focused on specific language outcomes to ensure feasibility; however, we acknowledge that many other important questions remain, including the role of repetition and word fluency in recovery, quality of life, and the impact of aphasia on (and interventions for) carers. Information on stroke lesion location and size were also excluded from the analysis. We included non-RCT and RCT data sets to support the research questions. Although non-RCT data sets pose a higher risk of bias (because of lack of randomisation), many of those we included were of high quality, reporting outcome assessor blinding and comparability of groups at baseline. The analysis prioritised IPD derived from RCT data sets, before we included IPD from non-RCT data sets. In analyses where RCT data was lacking, the non-RCT data provided an overview of the available data to date. Where RCT data was available to support the analysis, we found little indication of a difference in the findings (see *Chapters 4–7*).

**Methodological limitations**

Across the study, we undertook multiple subgroup analyses, and we acknowledge the risk of false-positive findings. The prespecified statistical analysis plan developed with the collaborators had a strong rationale for conducting the exploratory analyses in this way. We considered compensating for this risk statistically, but, given the exploratory approach, it was important to highlight all future research avenues. The findings should be interpreted in this context. The analysis approach could not consider or adjust for all possible confounders (e.g. dropout rates, interactions between age or severity and delivery of services). The examination of spontaneous recovery following aphasia in a natural history group was hampered by the lack of data availability. Ethically, it may be difficult to gather such data now in a clinically relevant population. Participants ranged from a few days to 38 years from stroke at study enrolment. We used the term 'study entry' to highlight this and controlled for time since stroke in the analysis. Despite these steps, it was not possible to distinguish spontaneous recovery of language from treatment-induced effects in the analysis. Aphasia researchers and therapists alike continue to work in this context.

**Interpretation of the data in relation to other research**

The results are in keeping with previous meta-analyses, although this IPD meta-analysis approach afforded a greater insight into the interactions between participant profile, therapy interventions and language outcomes than is possible in an aggregate data meta-analysis. Some meta-analyses were based on language-limited literature searching (e.g. English only),<sup>62-64</sup> included RCTs only,<sup>41</sup> included both RCT and non-RCT data sets,<sup>62</sup> and highlighted data availability limitations.<sup>41,62</sup>

Others have suggested the importance of early intervention after stroke,<sup>62,63</sup> reporting it to be twice as effective as spontaneous recovery.<sup>62</sup> Gains made later after stroke were acknowledged, but were smaller.<sup>62</sup> Some meta-analyses have suggested that  $\geq 2$  hours of SLT weekly is the optimal intensity,<sup>63</sup> whereas others indicated that this may be subtherapeutic and that a minimum of 9 hours of SLT weekly is required for gains.<sup>64</sup> Interventions that provided a total dosage in excess of 90 hours of therapy found benefits while those providing a dose of less than 44 hours did not.<sup>64</sup>

One review based on 23 case studies (57 participants), concluded that time since stroke was not a predictor of rehabilitation effect.<sup>127</sup> A 2016 Cochrane review update<sup>41</sup> found that intensive SLT benefited measures of overall language ability (group summary data from five RCTs) and functional language (two RCTs); however, these gains occurred alongside significantly higher numbers of dropouts from the intensive SLT compared with less intensive SLT approaches. They suggest that not all patients may be able to tolerate high-intensity SLT interventions for aphasia (4–15 hours per week).<sup>41</sup> A 2018 SLT RCT of an SLT intervention for aphasia did not experience the same level of dropout.<sup>26</sup>

**Patient and public involvement**

Stroke survivors, carers and health-care professionals identified enhanced interventions for people with aphasia as a research priority.<sup>49,73</sup> The RELEASE project sought to address this objective. The research plans were supported by organisations in the Aphasia Alliance (a UK collective of organisations supporting people with aphasia and their carers) and international counterparts (e.g. the Australian Aphasia Association). During the study, we worked closely with a group of people with aphasia and their carers based in Norwich (facilitated by Dr Simon Horton, University of East Anglia).

As a secondary data analysis project, the PPI involvement aim was not to inform the development of accessible information sheets, consent forms or appraise the acceptability of the intervention as might be expected in a primary research context,<sup>128,129</sup> but to facilitate communication of the findings to people with aphasia, their families, health-care professionals and commissioners. We scheduled a series of meetings with the group (at the project start, mid-way and on availability of the final results) during which we shared information in an accessible format prior to meetings, providing meeting updates and

opportunities for questions and comments arising. At the third and final meeting, we sought their input into future dissemination plans.

To date, the output from the group has included outlining possible routes to dissemination for people with aphasia, their families, health-care professionals and members of the public with an aphasia awareness-raising goal. Although the PPI group has had a limited influence on the secondary analysis methodologies (in keeping with the PPI aims), its input was vital to the dissemination planning stage. We will continue to seek their contribution to the development, interpretation and dissemination of the study findings. Working together with the PPI group ensures the relevance and accessibility of the findings. In addition, we will share our findings with commissioning groups in the UK. Communication with comparable international groups of people with aphasia, carers and health-care professionals will be facilitated by the RELEASE study collaborators and the Collaboration of Aphasia Trialists.

## Clinical implications

The limited insights into current SLT services for people with aphasia suggest that access to rehabilitation, in the context of the current evidence base, is inadequate. The findings of this study would support that assertion. The greatest language gains observed were associated with higher-dose SLT (frequency, duration, intensity and dosage) than has been described in recent reports of current practice,<sup>69</sup> raising the question of whether or not current levels of clinical intervention are subtherapeutic. Some subgroups of people with aphasia, however, may experience optimum language recovery in the context of SLT at lower or higher frequencies, intensities or dosage. Specific language gains may require high-intensity intervention more than others. High-quality RCTs are required to definitively address these questions.

Should these RCTs support the findings, it is unrealistic to expect that the intensity, duration and dosage that may be required for optimal language gains can be supported in the traditional model of SLT services, namely one-to-one, face-to-face contact with a qualified speech and language therapist.<sup>69</sup> Alternative approaches to the provision and augmentation of therapy intervention regimens developed and co-ordinated by qualified therapists could be investigated and their effectiveness evaluated.<sup>130</sup> In this context, face-to-face therapy sessions could continue to focus on specialist therapeutic tasks, assessment, prescription of home practice tasks, generalisation, training of family members to provide therapy and support language stimulation and conversational interactions.

We would welcome use of the augmented TIDieR classification framework developed during the course of this study to support the description of SLT interventions<sup>132</sup> in the development of future clinical guidelines to support, transparent and clinically implementable therapeutic intervention recommendations for aphasia after stroke.<sup>132</sup>

## Research implications

### *Further randomised controlled trials*

Targeted RCTs of aphasia treatment interventions are required to address the many uncertainties identified in the research. We noted many high-quality non-RCT data sets, which could have greatly reduced the risk of possible bias and increased confidence in the study findings with the application of a randomisation process on recruitment of the participants.

We noted the limited availability of data sets describing interventions that targeted improvements in reading comprehension and writing or reporting of reading and writing language outcomes. Greater research focus on these language domains is warranted.

A co-ordinated series of RCTs is required to definitively address the questions raised by this exploratory research and the possibility of a SLT–language recovery dose–response relationship. Researchers should specifically consider the development of participant inclusion criteria, subgroups of interest and experimental SLT interventions in the context of these findings. Understanding of complex rehabilitation interventions delivered to a complex population can be enhanced and methodologically addressed through improvements in research design, data capture, description and reporting, and the continuation of collaborative initiatives such as the RELEASE study.

### *Time since stroke at enrolment and clinical relevance*

We noted a trend towards better language scores with increasing time and across all domains among participants at study entry, which may suggest a risk of selection bias. Time since stroke was also a predictor of language recovery. Thus, time since aphasia onset should be considered in participant recruitment, interpretation of study findings and their clinical relevance.

### *Core data set*

The aphasia research community recently achieved international consensus on a core outcome set, but we also require consensus on a core data set that supports adequate description of participant demographics, stroke profile and, potentially, biomarkers, alongside a comprehensive measurement of language.

Similarly, advances made in the transparent reporting of complex interventions using the TIDieR checklist could be further enhanced when reporting complex SLT interventions by including a description of the language impairment target and the theoretical approach.<sup>132</sup> In the light of the findings from this study, details on tailoring of the SLT interventions to participants by functional relevance or level of difficulty, and the prescription of home-based practice tasks (and adherence to those practice tasks) would enhance the reporting of therapy dosage.

### *Legacy database*

This collaborative, international, multidisciplinary initiative has resulted in the creation of a large IPD database that (subject to approvals from the contributing research gatekeepers) will continue to support future secondary-analysis aphasia research activities.

## **Future research**

Future research targeting the evidence gaps identified in this comprehensive search, data extraction and analysis would be welcomed. The network meta-analysis highlights SLT treatment approaches lacking sufficient RCT comparisons.

Greater focus on the recruitment and documentation of non-English-speaking participants in aphasia research would enhance the representation of a clinically representative research population and provide greater insights into optimal rehabilitation approaches for people with aphasia in non-English languages and across more than one language. Greater involvement of multilingual and non-English speaking populations will require research investment in the development and validity of aphasia assessment tools for languages other than English. Supporting this endeavour would increase the international capacity for aphasia research activities, support recruitment of adequate sample sizes powered to address the research questions and inform clinical service development for non-English speaking and multilingual populations.

Recent trials have ensured that they achieved the requisite sample size and greater generalisability of the findings and engagement with the clinical speech and language therapists across multiple national sites.<sup>55,57</sup> Although international studies are increasingly common in the context of stroke rehabilitation, the linguistic and assessment restrictions to conducting aphasia research internationally represents a

specific challenge for aphasia rehabilitation researchers. Despite this, some [e.g. the Very Early Rehabilitation in Speech (VERSE) III trial<sup>72</sup>] have demonstrated the feasibility and benefits of an international recruitment strategy.

## Conclusions

The RELEASE study represents the largest aphasia research database developed to date, with collated IPD on demographics and language domains following a range of SLT interventions. The exploratory findings plotted the patterns of language recovery for people with aphasia who received SLT after stroke. Time since stroke, age, severity of aphasia at baseline and sex were found to be significantly associated with language recovery in selected domains. The best language gains from baseline across language domains were associated with SLT interventions at different levels of frequency, duration, intensity and dosage. The greatest language gains were seen in the context of SLT interventions that were delivered over several days a week, for several hours weekly, for a total of 20–50 hours. Exceptions to this pattern were typically associated with a small number of participants or data sets. Some subgroups may achieve higher language gains in the context of specific SLT interventions, but these exploratory findings require further definitive investigation to enhance the delivery of SLT for aphasia after stroke for the benefit of people with aphasia, their families and health-care professionals.



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## The RELEASE study database contributors

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- Dr Yiqiao Xin, NIHR Complex Review Support Unit, University of Glasgow.

For data synthesis methodological input:

- Dr Pauline Campbell, NMAHP Research Unit, Glasgow Caledonian University.

## Contributions of authors

**Marian C Brady** (<https://orcid.org/0000-0002-4589-7021>) conceived, designed and led the grant application and study; screened records, abstracts and full titles; extracted data; assessed the risk of bias; checked data extraction and risk of bias; and drafted and finalised the final report.

**Myzoon Ali** (<https://orcid.org/0000-0001-5899-2485>) was a co-applicant and contributor to the grant application, contributed to the statistical analysis, drafted *Chapter 4* and co-drafted *Chapter 5*.

**Kathryn VandenBerg** (<https://orcid.org/0000-0001-5035-9650>) and **Louise R Williams** (<https://orcid.org/0000-0003-2430-1142>) screened records, abstracts and full titles; retrieved papers; extracted data; and checked data extraction and risk of bias.

**Linda J Williams** (<https://orcid.org/0000-0002-6317-1718>) led and conducted the statistical analysis.

**Masahiro Abo** (<https://orcid.org/0000-0001-6701-4974>), **Frank Becker** (<https://orcid.org/0000-0002-0857-0628>), **Audrey Bowen** (<https://orcid.org/0000-0003-4075-1215>), **Caitlin Brandenburg** (<https://orcid.org/0000-0002-6992-7790>), **Caterina Breitenstein** (<https://orcid.org/0000-0002-6408-873X>), **Stefanie Bruehl** (<https://orcid.org/0000-0003-4826-1990>), **David A Copland** (<https://orcid.org/0000-0002-2257-4270>), **Tamara B Cranfill** (<https://orcid.org/0000-0001-7608-6443>), **Marie di Pietro-Bachmann** (<https://orcid.org/0000-0001-8027-2337>), **Pamela Enderby** (<https://orcid.org/0000-0002-4371-9053>), **Joanne Fillingham** (<https://orcid.org/0000-0002-0363-8021>), **Federica Lucia Galli** (<https://orcid.org/0000-0001-9244-9179>), **Marialuisa Gandolfi** (<https://orcid.org/0000-0002-0877-4807>), **Bertrand Glize** (<https://orcid.org/0000-0001-9618-2088>), **Erin Godecke** (<https://orcid.org/0000-0002-7210-1295>), **Katerina Hilari** (<https://orcid.org/0000-0003-2091-4849>), **Jacqueline Hinckley** (<https://orcid.org/0000-0002-4052-1420>), **Simon Horton** (<https://orcid.org/0000-0002-2133-1410>), **Petra Jaecks** (<https://orcid.org/0000-0002-5878-1327>), **Elizabeth Jefferies** (<https://orcid.org/0000-0002-3826-4330>), **Luis MT Jesus** (<https://orcid.org/0000-0002-8534-3218>), **Maria Kambanaros** (<https://orcid.org/0000-0002-5857-9460>), **Eun Kyoung Kang** (<https://orcid.org/0000-0001-5315-1361>), **Eman M Khedr** (<https://orcid.org/0000-0001-5679-9833>), **Anthony Pak-Hin Kong** (<https://orcid.org/0000-0002-6211-0358>), **Tarja Kukkonen** (<https://orcid.org/0000-0002-8189-0337>), **Marina Laganaro** (<https://orcid.org/0000-0002-4054-0939>), **Matthew A Lambon Ralph** (<https://orcid.org/0000-0001-5907-2488>), **Ann Charlotte Laska** (<https://orcid.org/0000-0002-7330-940X>), **Béatrice Leemann** (<https://orcid.org/0000-0003-2226-6777>), **Alexander P Leff** (<https://orcid.org/0000-0002-0831-3541>), **Roxele R Lima** (<https://orcid.org/0000-0002-9914-4789>), **Antje Lorenz** (<https://orcid.org/0000-0002-0200-1977>), **Brian MacWhinney** (<https://orcid.org/0000-0002-4988-1342>), **Rebecca Shisler Marshall** (<https://orcid.org/0000-0001-9313-5454>), **Flavia Mattioli** (<https://orcid.org/0000-0002-4912-5520>), **İlknur Maviş** (<https://orcid.org/0000-0003-3924-1138>), **Marcus Meinzer** (<https://orcid.org/0000-0003-1370-3947>), **Reza Nilipour** (<https://orcid.org/0000-0003-4180-7989>), **Enrique Noé** (<https://orcid.org/0000-0002-2547-8727>), **Nam-Jong Paik** (<https://orcid.org/0000-0002-5193-8678>), **Rebecca Palmer** (<https://orcid.org/0000-0002-2335-7104>), **Ilias Papatheanasiou** (<https://orcid.org/0000-0003-0999-696X>), **Brígida F Patrício** (<https://orcid.org/0000-0002-2619-470X>), **Isabel Pavão Martins** (<https://orcid.org/0000-0002-9611-7400>), **Cathy Price** (<https://orcid.org/0000-0003-0111-9364>), **Tatjana Prizl Jakovac** (<https://orcid.org/0000-0002-5018-9556>), **Elizabeth Rochon** (<https://orcid.org/0000-0001-5521-0513>), **Miranda L Rose** (<https://orcid.org/0000-0002-8892-0965>), **Charlotte Rosso** (<https://orcid.org/0000-0001-7236-1508>), **Ilona Rubi-Fessen** (<https://orcid.org/0000-0002-9775-3812>), **Marina B Ruiter** (<https://orcid.org/0000-0001-6147-5235>), **Claerwen Snell** (<https://orcid.org/0000-0001-8606-7801>), **Benjamin Stahl**

(<https://orcid.org/0000-0003-3957-1495>), Jerzy P Szaflarski (<https://orcid.org/0000-0002-5936-6627>), Shirley A Thomas (<https://orcid.org/0000-0003-0704-9387>), Mieke van de Sandt-Koenderman (<https://orcid.org/0000-0002-8104-6937>), Ineke van der Meulen (<https://orcid.org/0000-0002-6156-3873>), Evy Visch-Brink (<https://orcid.org/0000-0001-7833-0112>), Linda Worrall (<https://orcid.org/0000-0002-3283-7038>) and Heather Harris Wright (<https://orcid.org/0000-0001-6922-6364>) contributed IPD primary data.

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Simon Horton co-ordinated and facilitated PPI in the study.

Neil Hawkins (<https://orcid.org/0000-0003-3199-221X>) advised on the statistical analyses.

All authors were involved in interpretation of the results and reviewing and approving the final report.

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Brady MC, Ali M, VandenBerg K, Williams LJ, Williams LR, Abo M, *et al.* Communicating simply, but not too simply: reporting of participants and speech and language interventions for aphasia after stroke. *Int J Speech Lang Pathol* 2020;**22**:302–12.

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### Data-sharing statement

We will work with all data contributors to facilitate access to a version of the RELEASE study database. Access to each data set in the database was subject to the data-sharing agreement between the primary research team and the RELEASE study. Ethical agreements which supported sharing of some primary data sets, restricted access to those datasets solely for the purpose of informing the RELEASE study and analysis. Some data sets are separate databases in their own right (e.g. AphasiaBank, Cantonese Aphasia Bank and PLORAS<sup>119</sup>). Interested parties should approach those databases directly. Further information can be obtained from the corresponding author.

### Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

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## Appendix 1 Example search strategies

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### MEDLINE

MEDLINE (via Ovid).

Date range searched: 1946 to 22 September 2015.

Date searched: 22 September 2015.

### Search strategy

1. exp aphasia/
2. language disorders/or speech disorders/or anomia/
3. (aphasi\$ or dysphasi\$ or anomia or anomic).tw.
4. ((speech or language\$ or linguistic or communicat\$) adj5 (disorder\$ or impair\$ or problem\$ or dysfunction or difficult\$)).tw.
5. 1 or 2 or 3 or 4
6. exp aphasia/rh, th or language disorders/rh, th or speech disorders/rh, th or anomia/rh, th
7. speech-language pathology/or exp "rehabilitation of speech and language disorders"/
8. ((speech or language\$ or linguistic or aphasi\$ or dysphasi\$ or anomia or anomic) adj5 (therap\$ or train\$ or rehabilitat\$ or treat\$ or remediates\$ or intervention\$ or pathol\$)).tw.
9. (SLT or SLP).tw.
10. (melodic intonation therap\$ or MIT).tw.
11. 6 or 7 or 8 or 9 or 10
12. Randomized Controlled Trials as Topic/
13. random allocation/
14. Controlled Clinical Trials as Topic/
15. control groups/
16. clinical trials as topic/or clinical trials, phase i as topic/or clinical trials, phase ii as topic/or clinical trials, phase iii as topic/or clinical trials, phase iv as topic/
17. double-blind method/
18. single-blind method/
19. Placebos/
20. placebo effect/
21. cross-over studies/
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
25. (random\$ or RCT or RCTs).tw.
26. (controlled adj5 (trial\$ or stud\$)).tw.
27. (clinical\$ adj5 trial\$).tw.
28. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
29. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.

30. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
31. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
32. (cross-over or cross over or crossover).tw.
33. (placebo\$ or sham).tw.
34. trial.ti.
35. (assign\$ or allocat\$).tw.
36. controls.tw.
37. or/12-36
38. 5 and 11 and 37
39. exp animals/not humans.sh.
40. 38 not 39
41. (pediatric or paediatric or infant or infants or child or children\$ or childhood or neonat\$ or juvenile\$ or toddler\$).ti.
42. (child/or child, preschool/or adult children/or adolescent/or exp infant/) not exp adult/
43. 41 or 42
44. 40 not 43
45. 36 not 39.

## Cumulative Index to Nursing and Allied Health Literature

Cumulative Index to Nursing and Allied Health Literature (via EBSCOhost).

Date range searched: 1982 to 22 September 2015.

Date searched: 22 September 2015.

### Search strategy

1. (MH "Aphasia+")
2. (MH "Speech Disorders") or (MH "Language Disorders") or (MH "Anomia")
3. TI (aphasi\* or dysphasi\* or anomia or anomic) OR AB (aphasi\* or dysphasi\* or anomia or anomic)
4. TI ((speech or language\* or linguistic or communicat\*) N5 (disorder\* or impair\* or problem\* or dysfunction or difficult\*)) or AB ((speech or language\* or linguistic or communicat\*) N5 (disorder\* or impair\* or problem\* or dysfunction or difficult\*))
5. 1 OR 2 OR 3 OR 4
6. (MH "Aphasia+/RH/TH") or (MH "Speech Disorders/RH/TH ") or (MH "Language Disorders/RH/TH") or (MH "Anomia/RH/TH ")
7. (MH "Rehabilitation, Speech and Language") or (MH "Speech-Language Pathologists") or (MH "Speech-Language Pathology") or (MH "Speech Therapy+") or (MH "Language Therapy")
8. TI ((speech or language or linguistic or aphasi\* or dysphasi\* or anomia or anomic) N5 (therap\* or train\* or rehabilitat\* or treat\* or remediat\* or intervention\* or pathol\*)) or AB ((speech or language or linguistic or aphasi\* or dysphasi\* or anomia or anomic) N5 (therap\* or train\* or rehabilitat\* or treat\* or remediat\* or intervention\* or pathol\*))
9. TI (SLT or SLP) or AB (SLT or SLP)
10. TI (melodic intonation therap\* or MIT) or AB (melodic intonation therap\* or MIT)
11. 6 OR 7 OR 8 OR 9 OR 10
12. (MH "Randomized Controlled Trials") or (MH "Random Assignment") or (MH "Random Sample+")
13. (MH "Clinical Trials") or (MH "Intervention Trials") or (MH "Therapeutic Trials")
14. (MH "Double-Blind Studies") or (MH "Single-Blind Studies") or (MH "Triple-Blind Studies")
15. (MH "Control (Research)") or (MH "Control Group") or (MH "Placebos") or (MH "Placebo Effect")
16. (MH "Crossover Design") OR (MH "Quasi-Experimental Studies")

17. PT (clinical trial or randomized controlled trial)
18. TI (random\* or RCT or RCTs) or AB (random\* or RCT or RCTs)
19. TI (controlled N5 (trial\* or stud\*)) or AB (controlled N5 (trial\* or stud\*))
20. TI (clinical\* N5 trial\*) or AB (clinical\* N5 trial\*)
21. TI ((control or treatment or experiment\* or intervention) N5 (group\* or subject\* or patient\*)) or AB ((control or treatment or experiment\* or intervention) N5 (group\* or subject\* or patient\*))
22. TI ((control or experiment\* or conservative) N5 (treatment or therapy or procedure or manage\*)) or AB ((control or experiment\* or conservative) N5 (treatment or therapy or procedure or manage\*))
23. TI ((singl\* or doubl\* or tripl\* or trebl\*) N5 (blind\* or mask\*)) or AB ((singl\* or doubl\* or tripl\* or trebl\*) N5 (blind\* or mask\*))
24. TI (cross-over or cross over or crossover) or AB (cross-over or cross over or crossover)
25. TI (placebo\* or sham) or AB (placebo\* or sham)
26. TI trial
27. TI (assign\* or allocat\*) or AB (assign\* or allocat\*)
28. TI controls or AB controls
29. TI (quasi-random\* or quasi random\* or pseudo-random\* or pseudo random\*) or AB (quasi-random\* or quasi random\* or pseudo-random\* or pseudo random\*)
30. 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. 5 AND 11 AND 30
32. TI (pediatric or paediatric or infant or infants or child or children\* or childhood or neonat\* or juvenile\* or toddler\*)
33. ((MH "Adolescence+") or (MH "Child+") or (MH "Infant+")) not (MH "Adult")
34. 32 OR 33
35. 31 not 34



## Appendix 2 Transformation process

Non-anchor measures were transformed into a format that could be compared with the chosen anchor measure using the formula in Box 4.

With thanks to Professor Jon Godwin, Glasgow Caledonian University, for an earlier version of this formula, which he reported as regularly being used by the Early Breast Cancer Trialists Group (2018, personal communication). The version above has been further adapted by Dr Linda J Williams, University of Edinburgh.

### BOX 4 Linear quartile transformation

$X_{\text{anchor}}$  is an observation transformed into the anchor measurement instrument.

$X_{\text{minority}}$  is an observation measured on the non-anchor (minority) measurement instrument.

If we consider the data in the anchor measure and minority measure to be a series of quartiles, such that  $Q_0$  = minimum,  $Q_1$  = lower quartile,  $Q_2$  = median,  $Q_3$  = upper quartile and  $Q_4$  = maximum, then we can linearly transform each  $X_{\text{minority}}$  value to within its corresponding quartile in the anchor measure.

If  $X_{\text{minority}}$  lies between  $\text{Minority}_{Q_n}$  and  $\text{Minority}_{Q_{n+1}}$ , then we can transform the data thus:

$$Y = (\text{Anchor}_{Q_{n+1}} - \text{Anchor}_{Q_n}) / (\text{Minority}_{Q_{n+1}} - \text{Minority}_{Q_n}) \quad (1)$$

and

$$X_{\text{anchor}} = \text{Anchor}_{Q_{n+1}} + (X_{\text{minority}} - \text{Minority}_{Q_{n+1}}) \times Y. \quad (2)$$

However, if  $\text{Minority}_{Q_n} = \text{Minority}_{Q_{n+1}}$ , then  $X_{\text{anchor}} = (\text{Anchor}_{Q_{n+1}} + \text{Anchor}_{Q_n}) / 2. \quad (3)$

#### Example

The anchor measure for overall severity was chosen to be the WAB-AQ. So the anchor quartiles are as follows:

$Q_0 = 0$ ,  $Q_1 = 56.3$ ,  $Q_2 = 64.9$ ,  $Q_3 = 89.4$  and  $Q_4 = 100$ .

Suppose we have a data point from the NGA data set of 80, for which the minority quartiles are as follows:

$Q_0 = 0$ ,  $Q_1 = 64$ ,  $Q_2 = 110$ ,  $Q_3 = 161$  and  $Q_4 = 217$ .

We find that 80 lies between  $Q_1 = 64$  and  $Q_2 = 110$  in the minority measure, with the corresponding anchor  $Q_1 = 56.3$  and  $Q_2 = 64.9$ .

Therefore,  $Y = (64.9 - 56.3) / (110 - 64) = 8.6 / 46 = 0.1870$ .

On the anchor scale,  $X_{\text{anchor}} = 64.9 + (80 - 110) \times 0.1870 = 64.9 - 5.6 = 59.3$ .

---

NGA, Norsk Grunntest for Afasi.



## Appendix 3 Logic models

(a)

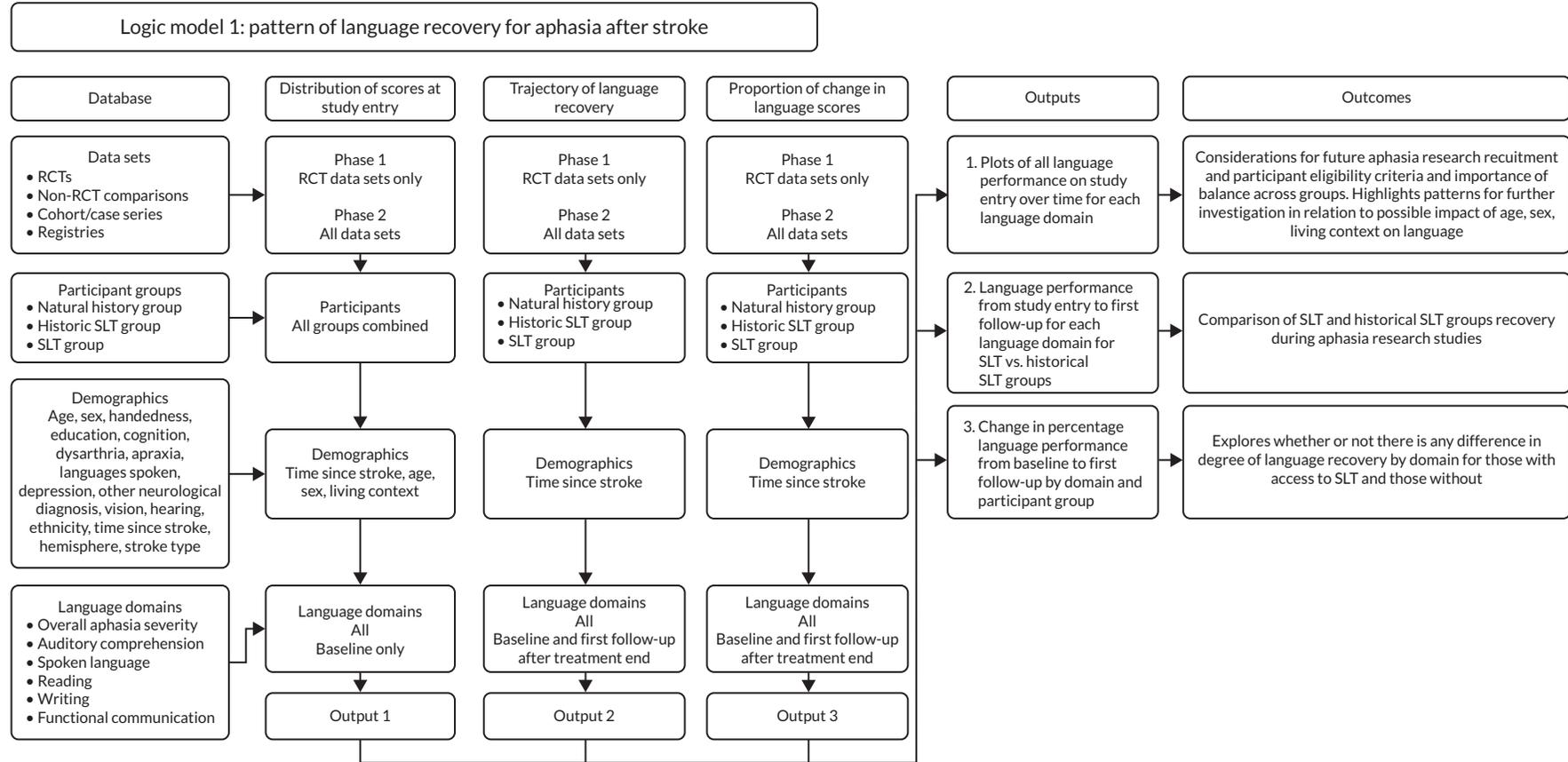


FIGURE 26 Logic models 1-4. (a) Logic model 1; (b) logic model 2; (c) logic model 3; and (d) logic model 4. (continued)

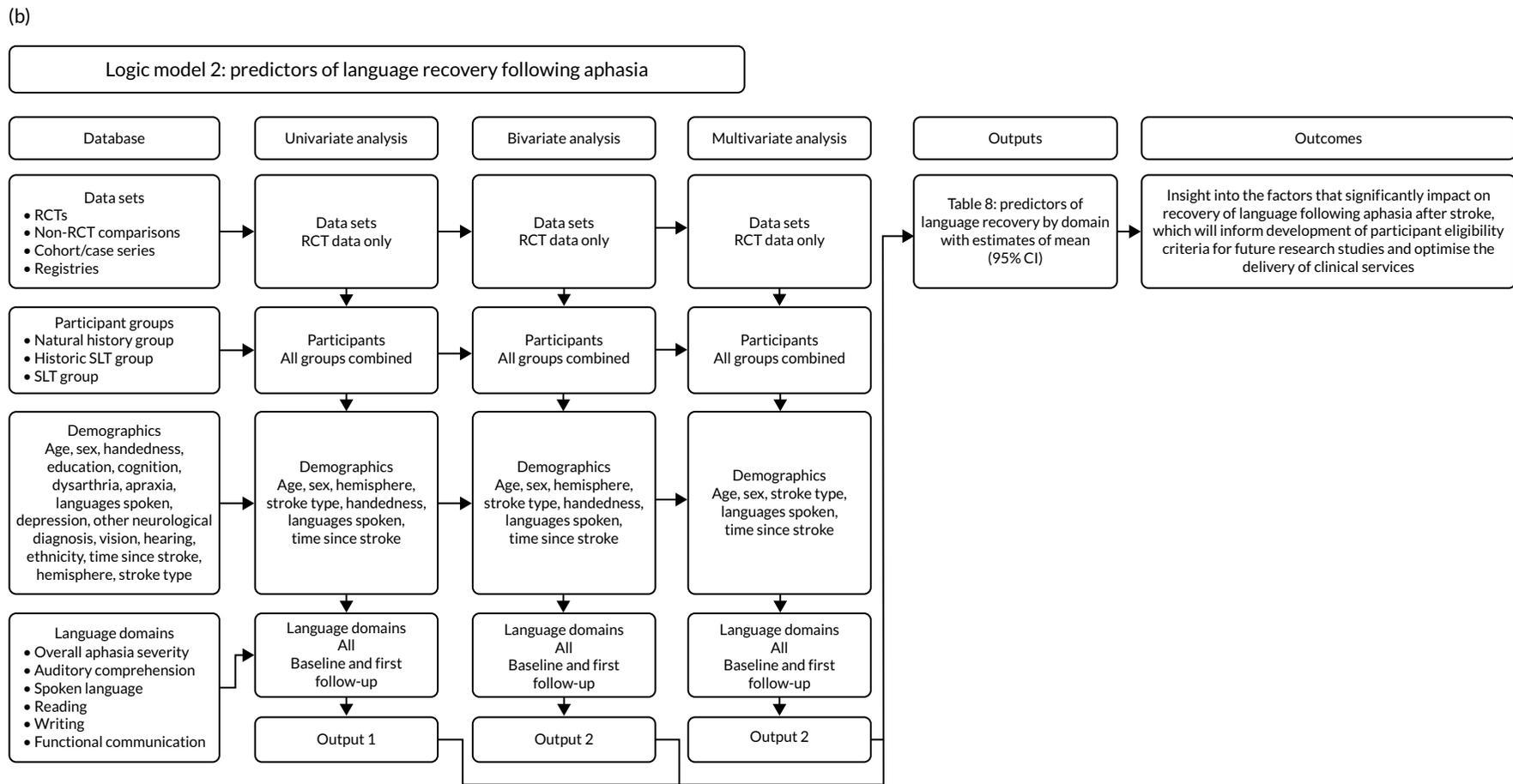


FIGURE 26 Logic models 1–4. (a) Logic model 1; (b) logic model 2; (c) logic model 3; and (d) logic model 4. (continued)

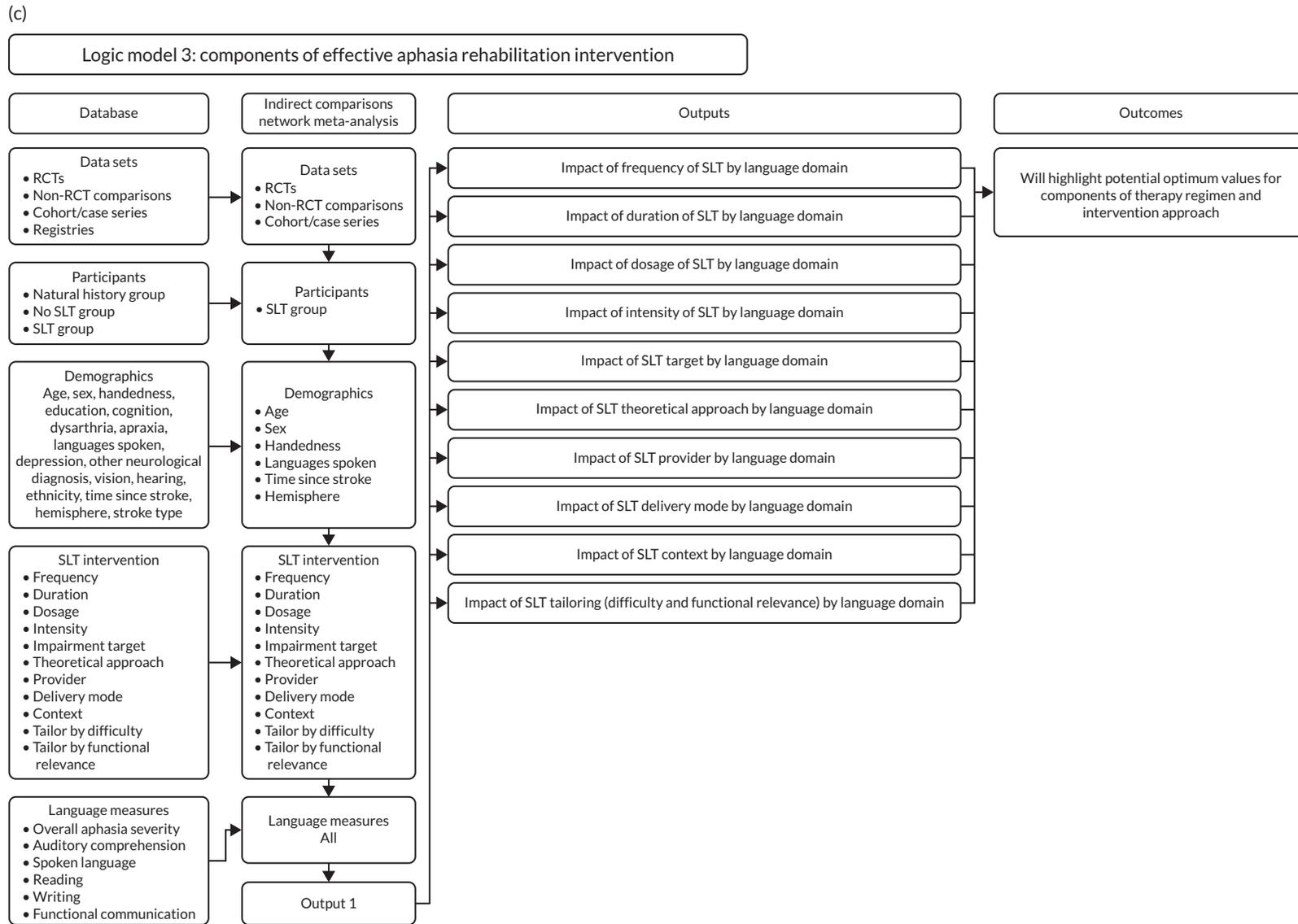


FIGURE 26 Logic models 1–4. (a) Logic model 1; (b) logic model 2; (c) logic model 3; and (d) logic model 4. (continued)

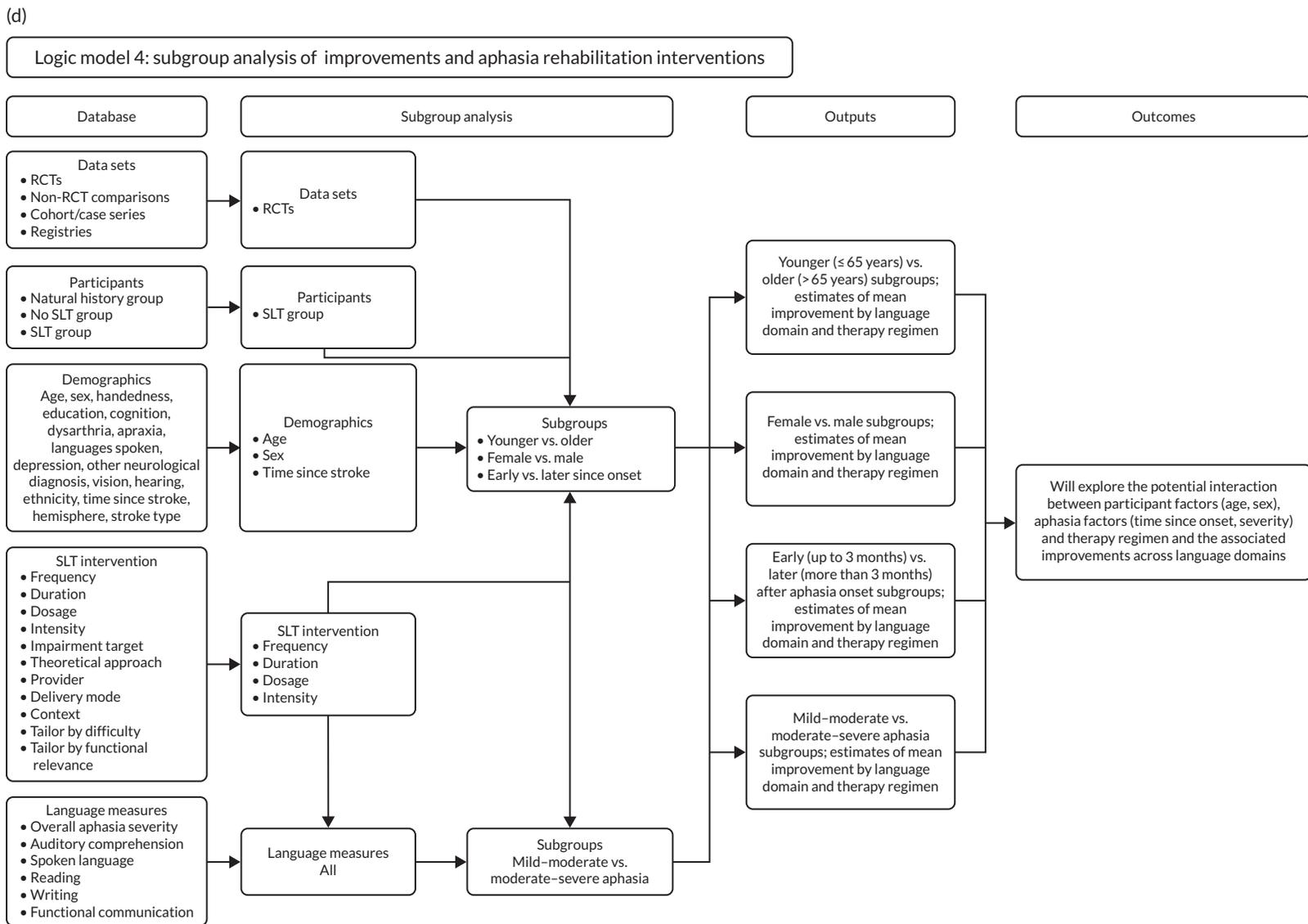


FIGURE 26 Logic models 1–4. (a) Logic model 1; (b) logic model 2; (c) logic model 3; and (d) logic model 4.



## Appendix 4 Between-group comparisons (randomised controlled trials)

TABLE 12 Between-group comparison of demographics at baseline, RCT data sets

Study	Treatment group	Number of participants in each group allocation	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transformed score, median (IQR)	Wilcoxon signed-rank test <sup>134</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>133</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>134</sup> for years of education differences between groups (p-value)
002	A	44	76 (67.5–81)	0.72	25 (56.8)	0.90	6 (2.5–8)	0.66	-	-	-	-	-	-
	B	45	76 (67–82)		25 (55.6)		6 (3–8)		-	-	-	-	-	-
003	A	64	75.5 (66–84)	0.23	33 (53.2)	0.08	3 (2–4)	0.19	57.1 (28.2–64.4)	0.78	-	-	-	-
	B	61	79 (72–85)		23 (37.7)		3 (2–4)		58.0 (28.2–64.7)		-	-	-	-
004	A	77	71 (63–78)	0.60	42 (54.6)	0.81	12 (9–16)	0.73	-	-	-	-	-	-
	B	76	72 (63–78.5)		40 (52.6)		11 (9–18)		-	-	-	-	-	-
006	A	5	55 (47–66)	0.37	4 (80)	0.49	1887 (1745–2092)	0.84	-	-	5 (100)	-	10 (10–16)	0.68
	B	5	48 (45–53)		3 (60)		2259 (1871–2478)		-	-	5 (100)	-	16 (9–19)	
008	A	17	71 (65–80)	0.30	9 (52.9)	0.29	2031.5 (1096–3127)	0.53	-	-	-	-	-	-
	B	17	66 (53–76)		12 (70.6)		2042 (1761–3512)		-	-	-	-	-	-
010	A	15	70 (64–74)	0.54	5 (83.3)	0.63	426 (365–609)	0.36	-	-	15 (100)	-	4.5 (4–5)	0.16
	B	17	67 (56–73)		11 (73.3)		183 (91–914)		-	-	17 (100)	-	5 (5–7)	
011a	A	6	45 (28–57)	0.29 <sup>a</sup>	5 (83.3)	0.43	106.5 (30–244)	0.88	75.9 (71.4–81.2)	0.67 <sup>a</sup>	6 (100)	0.37	-	-
	B	7	55 (52–63)		6 (85.7)		61 (30–61)		73.8 (55.9–80.3)		7 (100)		-	-
	C	5	52 (47–54)		3 (60)		152 (61–152)		72.1 (58.1–90.1)		5 (100)		-	-
	D	6	56 (48–58)		3 (50)		91 (61–152)		65.7 (59.2–72.1)		5 (83.3)		-	-
011c	A	6	55.5 (49–63)	1.0	5 (83.3)	0.51	61 (30–122)	0.48	39.4 (35.4–47.8)	0.44	6 (100)	-	-	-
	B	6	53.5 (49–62)		4 (66.7)		121.5 (30–335)		48.7 (42.7–56.3)		6 (100)		-	-
015	A	72	55 (46.5–60)	0.70	49 (68.1)	0.24	822.5 (396–1462)	0.056	70.4 (40.7–87.9)	0.80	67 (93.1)	0.29	10 (10–17)	0.17
	B	70	54 (50–61)		41 (58.6)		1263.5 (487–2071)		67.2 (44.1–84.8)		64 (91.4)		10 (10–10)	
016	A	6	69.5 (63–75)	0.53	4 (66.7)	0.56	2.5 (2–3)	1.00	-	-	6 (100)	-	8 (5–8)	0.33
	B	6	61.5 (59–72)		3 (50)		2 (2–3)		-	-	6 (100)		5 (5–8)	
022	A	51	72 (57–79)	0.24	29 (56.9)	0.22	264 (125–782)	0.52	-	-	-	-	-	-
	B	54	67.5 (55–75)		37 (68.5)		275 (149–1172)		-	-	-	-	-	-

Study	Treatment group	Number of participants in each group allocation	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transformed score, median (IQR)	Wilcoxon signed-rank test <sup>134</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>133</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>134</sup> for years of education differences between groups (p-value)
023	A	32	72.5 (62.5–79)	0.52	14 (43.8)	0.37	2.5 (2–4)	0.59	31 (9.75–54.5)	<b>0.045</b>	-	-	-	-
	B	27	67 (58–79)		15 (55.6)		3 (2–4)		9 (0–34.1)		-	-	-	-
024	A	17	65 (57–71)	0.23	10 (58.8)	0.10	105 (56–126)	0.28	74.9 (42–87.3)	0.54	-	-	-	-
	B	14	69.5 (59–74)		12 (85.7)		175 (70–364)		55.3 (34.2–87.7)		-	-	-	-
025	A	14	55.5 (50–67)	0.11	9 (64.3)	0.48	1141.5 (426–2223)	0.75	-	-	14 (100)	0.20	-	-
	B	10	51.5 (41–54)		5 (50)		913.5 (335–2101)		-		8 (88.9)		-	-
026	A	9	72 (64–77)	0.23 <sup>a</sup>	4 (44.4)	0.50	7 (7–7)	1.00 <sup>a</sup>	56.3 (0–81.2)	0.46	9 (100)	-	6.5 (6.5–6.5)	0.80 <sup>a</sup>
	B	8	63 (58.5–69)		4 (50)		7 (7–7)		60.6 (56.3–81.2)		8 (100)		6.5 (6.5–6.5)	
	C	9	64 (61–72)		7 (77.8)		7 (7–7)		64.9 (56.3–64.9)		9 (100)		6.5 (4–6.5)	
	D	10	66.5 (59–75)		6 (60)		7 (7–7)		56.3 (0–64.9)		10 (100)		6.5 (4–6.5)	
027	A	15	57 (51–72)	0.12	10 (66.7)	0.70	56 (42–70)	0.74	29 (11.5–67.9)	0.62	15 (100)	-	4 (4–9)	0.96
	B	15	64 (58–71)		9 (60)		42 (28–70)		43.1 (16.3–64.7)		15 (100)		4 (4–9)	
028	A	10	65.5 (56–69)	<b>0.02</b>	9 (90)	0.26	1324.5 (1066–1797)	0.059	-	-	-	-	11 (9–13)	1.00
	B	10	47.5 (43–61)		7 (70)		913.5 (548–1035)		-		-		11 (9–13)	
035	A	8	64.3 (56.4–70)	0.57	4 (50)	1.00	360.5 (345–383.5)	0.19	-	-	7 (87.5)	0.25	9 (6–10)	0.40
	B	10	67.4 (56.3–74.3)		5 (50)		373.5 (367–447)		-		10 (100)		7.5 (6–9)	
038	A	10	56.5 (51–61)	0.34	5 (50)	0.68	28 (14–35)	0.37	28.2 (0–56.3)	0.72	10 (100)	-	-	-
	B	19	61 (54–68)		8 (42.1)		28 (14–56)		0 (0–56.3)		19 (100)		-	-
041	A	7	68 (56–77)	0.32	5 (71.4)	0.48	639 (365–700)	0.85	-	-	-	-	-	-
	B	4	61.5 (37–67.5)		2 (50)		1020 (441.5–1446.5)		-		-		-	-
054	A	38	68 (62–78)	0.95	14 (36.8)	0.07	22.5 (17–26)	0.95	-	-	31 (81.6)	0.35	12 (12–13)	0.55
	B	42	69.5 (57–79)		24 (57.1)		22 (19–24)		-		35 (85.4)		12 (12–13)	
056	A	35	60 (52–71)	-	16 (45.7)	-	94 (87–99)	-	64.9 (56.3–89.4)	-	32 (94.1)	-	12 (11–15)	-
060	A	28	64.9 (58.7–73.9)	0.075	18 (64.3)	0.34	116.5 (102.5–145)	1.00	-	-	25 (89.3)	0.36	12 (8–14)	0.94
	B	29	58.3 (50.1–69.1)		15 (51.7)		115 (101–147)		-		27 (93.1)		12 (10–14)	

continued

TABLE 12 Between-group comparison of demographics at baseline, RCT data sets (continued)

Study	Treatment group	Number of participants in each group allocation	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transformed score, median (IQR)	Wilcoxon signed-rank test <sup>134</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>133</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>134</sup> for years of education differences between groups (p-value)
065	A	5	60 (56–67)	1.00	4 (80)	–	1328 (313–5040)	0.24	66 (58.5–91.2)	–	5 (100)	–	9 (9–12)	0.09
	B	5	65 (60–66)		4 (80)		213 (180–241)		59.5 (58.5–64.1)		5 (100)		16 (12–16)	
067	A	18	54 (49–61)	0.98	11 (61.1)	0.22	106.5 (61–1127)	0.71	–	–	18 (100)	0.40	15 (13–15)	0.20
	B	26	55.5 (48–61)		11 (42.3)		61 (61–548)		–	–	25 (96.2)		13 (10–15)	
069	Multimodal therapy	26	60.5 (48–67)	–	15 (57.7)	–	700.5 (457–1583)	–	–	–	–	–	16 (14–18)	–
076	A	15	67 (65–73)	0.71	9 (60)	0.14	47 (28–69)	0.37	–	–	15 (100)	–	–	–
	B	15	70 (59–47)		5 (33.3)		38 (24–56)		–	–	15 (100)		–	–
078	A	11	63 (61.4–67.8)	0.55	11 (100)	<b>0.038</b>	1242 (438–2703)	0.55	–	–	9 (81.8)	0.18	–	–
	B	9	62.4 (50.2–66.5)		6 (66.7)		657 (438–1863)		–	–	9 (100)		–	–
081	A	8	57.5 (53.5–66.5)	0.97	7 (87.5)	0.19	853 (365.5–3014.5)	0.12	–	–	–	–	14 (12.5–15)	0.99
	B	12	54.5 (49.5–69)		6 (50)		213.5 (122–594)		–	–	–	–	13 (9.5–16)	
	C	18	61 (48–67)		13 (72.2)		198 (152–1248)		–	–	–	–	14 (11–16)	
085	A	12	74.5 (53–83.5)	0.76	9 (75)	0.09	5 (4–8)	0.38	45.5 (14.6–70.4)	0.62	–	–	–	–
	B	8	76.5 (65.5–82.5)		3 (37.5)		6.5 (4.5–8.5)		51.1 (17.7–68.1)		–	–	–	–
301	NA	16	53 (43–57.5)	–	15 (93.8)	–	244 (183–883)	–	–	–	–	–	–	–
312	A	10	54 (49–64)	0.89	6 (60)	0.25	2375 (1157–5237)	<b>0.024</b>	–	–	8 (80)	0.76	10 (10–13)	0.57
	B	7	56 (48–62)		6 (85.7)		457 (305–1370)		–	–	6 (85.7)		10 (9–13)	
313	A	71	70 (65–75)	<b>0.007</b>	38 (53.5)	0.45	28 (28–49)	0.18	–	–	–	–	–	–
	B	84	67 (59–72)		50 (59.5)		35 (28–49)		–	–	–	–	–	–
316	A	20	58.5 (54–69.5)	0.53	10 (50)	0.53	28.5 (18–51)	0.39	56.3 (56.3–73.1)	0.40	20 (100)	–	12 (10–13)	0.095
	B	20	67 (51.5–71.5)		8 (40)		26.5 (15.5–47.5)		64.9 (56.3–81.2)		20 (100)		13.5 (11–16)	
330	A	14	53.5 (50–60)	<b>0.038</b>	7 (50)	0.25	548 (402–913)	<b>0.013</b>	–	–	14 (100)	–	–	–
	B	14	46 (43–48)		10 (71.4)		1315 (767–3653)		–	–	14 (100)		–	–

Study	Treatment group	Number of participants in each group allocation	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transformed score, median (IQR)	Wilcoxon signed-rank test <sup>134</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>133</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>134</sup> for years of education differences between groups (p-value)
334	A	10	65 (52–72)	0.20	7 (70)	0.33	66 (42–103)	0.17	64.9 (56.3–64.9)	0.95	10 (100)	-	12.5 (10–14)	0.30
	B	14	56 (54–60)		7 (50)		46 (28–76)		64.9 (56.3–64.9)		14 (100)		14 (12–17)	
339	A	24	58 (51.5–68.5)	-	13 (54.2)	-	837.5 (456.5–1553)	-	66.3 (55.2–83.4)	-	-	-	16 (14–16)	-
345	A	7	66 (62–80)	0.40 <sup>a</sup>	3 (42.9)	0.56	23 (20–30)	0.71 <sup>a</sup>	48 (9.9–58.4)	0.50 <sup>a</sup>	7 (100)	-	9 (9–12)	0.61 <sup>a</sup>
	B	7	65 (49–78)		4 (57.1)		23 (20–35)		57.8 (19–58.1)		7 (100)	-	12 (9–16)	
	C	7	64 (55–72)		5 (71.4)		22 (18–35)		38.1 (20.7–48.8)		7 (100)	-	12 (9–16)	
357	A	5	59 (53–64)	0.47 <sup>a</sup>	2 (40)	0.06	1462 (1279–1675)	0.15 <sup>a</sup>	81.2 (64.9–81.2)	0.59	-	-	-	-
	B	6	58 (45–62)		5 (83.3)		639.5 (365–1309)		81.2 (81.2–81.2)		-	-	-	-
	C	6	51 (36–63)		6 (100)		381 (183–639)		81.2 (81.2–81.2)		-	-	-	-
382	NA	12	62 (56.5–70)	-	10 (83.3)	-	334.5 (274–1095.5)	-	49.1 (31.4–74.2)	-	12 (100)	-	-	-
383	NA	12	49.5 (34.5–54)	-	6 (50)	-	334.5 (197.5–958.5)	-	-	-	12 (100)	-	-	-
388	NA	12	62 (52.5–65)	-	8 (66.7)	-	1263 (593.5–1628.5)	-	-	-	12 (100)	-	-	-
392	A	6	62 (54–66)	0.28	4 (66.7)	0.51	1218 (914–1614)	0.70	-	-	6 (100)	-	13 (10–16)	0.94
	B	6	68.5 (63–72)		5 (83.3)		1111.5 (822–1462)		-	-	6 (100)	-	13 (12–14)	
401	A	10	69 (57–79)	-	8 (80)	-	1279 (548–1553)	-	-	-	-	-	13.5 (12–16)	-
410	NA	10	61 (60–65)	-	7 (100)	-	1628.5 (883–2527)	-	-	-	-	-	17 (14–18)	-
416	NA	10	67.5 (58–75)	-	5 (50)	-	1537 (426–1948)	-	-	-	10 (100)	-	13 (12–16)	-
471	NA	16	-	-	-	-	365 (152–623.5)	-	81.2 (81.2–92.9)	-	16 (100)	-	-	-
520	NA	12	52 (45–59.5)	-	7 (58.3)	-	2206 (1354–3210)	-	-	-	12 (100)	-	14 (10.5–17)	-

NA, not applicable.

a Owing to the distribution of the data, the Kruskal-Wallis test was used for these specific comparisons in preference to the Wilcoxon signed rank test.

Shading indicates significant results.



## **Appendix 5** Between-group comparisons (non-randomised controlled trials)

TABLE 13 Between-group comparison of demographics at baseline, non-RCT data sets

Study ID	Group allocation	n	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transform score, median (IQR)	Wilcoxon two sample t-test <sup>133</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>134</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for years of education differences between groups (p-value)
001	-	119	77 (71-82)	-	64 (53.8)	-	5 (3-8)	-	65.1 (56.3-89.4)	-	106 (93)	-	-	-
005	-	301	63.5 (54.7-70.8)	-	183 (60.8)	-	1442.5 (694-2622.5)	-	-	-	273 (90.7)	-	16 (13-17)	-
007	-	50	65.5 (58-71)	-	36 (73.5)	-	15 (15-15)	-	-	-	-	-	-	-
009	-	25	55 (46-67)	-	13 (52)	-	487.2 (182.7-791.7)	-	-	-	-	-	8 (4-11)	-
011b	SLT	18	48.5 (43-56)	-	12 (66.7)	-	91 (61-183)	-	40.6 (37.5-53.5)	-	13 (100)	-	-	-
013	-	23	52 (43-66)	-	14 (60.9)	-	365 (274-761)	-	-	-	-	-	13 (8-17)	-
014	-	12	70 (66.5-73.5)	-	8 (66.7)	-	913.5 (731-1826)	-	-	-	12 (100)	-	5 (2.5-6)	-
018	-	32	73 (61-78.5)	-	20 (62.5)	-	14 (14-14)	-	-	-	-	-	-	-
019	-	16	57 (52.7-63.2)	-	9 (56.3)	-	103.5 (67.5-184.5)	-	63.7 (33.2-87.2)	-	16 (100)	-	12 (11-13)	-
020	-	14	62.5 (52.4-68.6)	-	10 (71.4)	-	146.5 (122-179)	-	72.5 (47.8-87.2)	-	14 (100)	-	14 (11-17)	-
021	-	39	55.5 (46.2-61.9)	-	21 (53.9)	-	94 (64-118)	-	70.1 (42.3-86.9)	-	-	-	11 (11-16)	-
029	-	19	70 (62-76)	-	11 (57.9)	-	152 (122-152)	-	-	-	19 (100)	-	5 (5-8)	-
030	A	53	81 (69-87)	0.39	22 (41.5)	0.29	6 (2-12)	< 0.0001	-	-	-	-	-	-
	B	42	77 (66-84)		22 (52.4)		22 (8-29)		-	-	-	-	-	-
033	-	50	65 (56-73)	-	28 (56)	-	2192 (1096-3287)	-	-	-	-	-	-	-
034	-	83	65 (51-74)	-	52 (62.7)	-	1096 (398-1501)	-	-	-	-	-	-	-
036	-	12	57.5 (48.5-66)	-	7 (58.3)	-	988.5 (713-1398.5)	-	65.7 (55.9-89.3)	-	-	-	-	-
037	-	50	69.5 (62-80)	-	30 (60)	-	346 (225-468)	-	-	-	45 (90)	-	-	-
039	A	16	54 (50.5-67)	0.25	14 (87.5)	0.46	807 (411-1796)	0.11	48.8 (37.1-66.9)	0.82	15 (93.8)	0.62	-	-
	B	18	59 (54-71)		14 (77.8)		487 (365-670)		44.5 (41.1-61.3)		16 (88.9)		-	-
040	-	15	65 (55-72)	-	7 (46.7)	-	1736 (457-2893)	-	62.6 (57.6-89.4)	-	-	-	14 (12-16)	-
042	-	13	59 (48-62)	-	7 (53.9)	-	59 (19-172)	-	45.7 (40.3-51)	-	-	-	12 (11-14)	-
043	-	10	48 (43-51)	-	7 (70)	-	411 (274-609)	-	-	-	7 (100)	-	-	-
045	SLT	13	47 (44-58)	-	10 (71.4)	-	1233 (761-1492)	-	-	-	14 (100)	-	10 (9-13)	-
047	-	70	67 (56-74)	-	53 (75.7)	-	1157.5 (670-2101)	-	81.2 (64.9-92.9)	-	70 (100)	-	11 (11-13)	-

Study ID	Group allocation	n	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transform score, median (IQR)	Wilcoxon two sample t-test <sup>133</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>134</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for years of education differences between groups (p-value)
048	A	3	62 (58–66)	0.28 <sup>a</sup>	3 (100)	0.04	1462 (457–3502)	0.38 <sup>a</sup>	58.9 (37.2–87.2)	0.86 <sup>a</sup>	3 (100)	-	-	-
	B	5	53 (46–67)		3 (60)		1188 (853–1188)		45.5 (18–100)		5 (100)		-	
	C	11	55 (46–59)		11 (100)		914 (639–1218)		69.2 (43.6–85.5)		11 (100)		-	
	D	5	58 (51–63)		5 (100)		792 (548–822)		78.5 (75–92.9)		5 (100)		-	
049	-	86	70 (59–79)	-	45 (52.3)	-	14 (14–14)	-	56.3 (0–81.2)	-	86 (100)	-	-	-
050	-	420	62 (51.8–70.7)	-	298 (71)	-	1091.5 (491–2375.5)	-	71.5 (42.6–87.3)	-	370 (88.1)	-	11 (11–16)	-
052	A	7	62 (33–80)	0.82	3 (42.9)	0.18	61 (61–91)	0.04	-	-	-	-	-	-
	B	3	54 (51–54)		0 (0)		183 (183–3654)		-		-		-	
053	A	5	56 (53–64)	1.00	3 (60)	0.74	670 (670–1218)	0.33	-	-	5 (100)	-	16 (15–17)	0.11
	B	6	61.5 (49–66)		3 (50)		1400.5 (761–2345)		-		6 (100)		15 (13–15)	
057	-	51	52 (43–64)	-	26 (51)	-	442 (61–1087)	-	-	-	51 (100)	-	12 (12–14.5)	-
058	-	10	57 (51–64)	-	5 (50)	-	56 (49–70)	-	-	-	8 (80)	-	10 (10–14)	-
059	A	5	65 (56–67)	0.42	2 (40)	0.20	183 (122–487)	1.00	-	-	5 (100)	-	-	-
	B	5	56 (52–66)		3 (60)		183 (122–244)		-		5 (100)		-	
061	-	24	71 (59–80.5)	-	10 (41.7)	-	152 (30–609)	-	-	-	-	-	12 (12–16)	-
062	-	11	73 (64–74)	-	9 (81.8)	-	-	-	-	-	-	-	-	-
063	-	13	65 (58–69)	-	8 (61.5)	-	883 (365–2040)	-	-	-	13 (100)	-	-	-
064	-	16	49.5 (46.5–60.5)	-	10 (62.5)	-	80 (49.5–487.5)	-	77.2 (64.9–89.4)	-	15 (93.8)	-	-	-
066	-	53	60 (52.67)	-	41 (77.4)	-	213 (91–502.5)	-	65.7 (56.3–89.4)	-	-	-	8 (5–12)	-
068	-	47	56 (51–62)	-	30 (63.8)	-	1035 (244–1614)	-	59.5 (56.7–91.1)	-	43 (91.5)	-	12 (8–14)	-
069	A	26	60.5 (48–67)	-	15 (57.7)	-	700.5 (457–1583)	-	-	-	-	-	16 (14–18)	-
070	-	147	70 (58–79)	-	69 (46.9)	-	8 (8–8)	-	-	-	127 (88.2)	-	12 (12–14)	-
071	-	258	60.5 (49.8–69.9)	-	172 (66.7)	-	94 (37–213)	-	-	-	255 (99.6)	-	8 (8–12)	-
072	-	26	49 (44–64)	-	17 (65.4)	-	40 (15–326)	-	81.2 (60.6–89.4)	-	-	-	-	-

continued

TABLE 13 Between-group comparison of demographics at baseline, non-RCT data sets (continued)

Study ID	Group allocation	n	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transform score, median (IQR)	Wilcoxon two sample t-test <sup>133</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>134</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for years of education differences between groups (p-value)
073	-	19	74 (67-80)	-	11 (61.1)	-	2740.5 (1918.5-3380)	-	-	-	-	-	11 (10-11)	-
074	-	15	64 (51-75)	-	-	-	122 (76-274)	-	64.9 (56.3-81.2)	-	15 (100)	-	-	-
077	-	97	65 (53-71)	-	60 (61.9)	-	20 (10-35)	-	64.9 (56.3-89.4)	-	90 (98.9)	-	12 (9-16)	-
079	-	105	54 (48-60)	-	70 (66.7)	-	1010 (422-2505)	-	64.9 (56.3-89.4)	-	105 (100)	-	9 (6-11)	-
080	-	30	65.5 (56-71)	-	15 (50)	-	167.5 (64-279)	-	64.8 (52.7-83.2)	-	25 (83.3)	-	8.5 (0-12)	-
082	-	14	63 (55-65)	-	10 (71.4)	-	30 (16-57)	-	-	-	14 (100)	-	12 (8-13)	-
083	-	10	61 (52-71)	-	6 (60)	-	1369.5 (913-4383)	-	-	-	10 (100)	-	13.5 (12-18)	-
084	-	35	62 (57-70)	-	22 (62.9)	-	1340 (579-2710)	-	77.8 (42.8-88.5)	-	32 (91.4)	-	11 (9-12)	-
086	A	5	65 (47-71)	1.01	3 (60)	0.77	304 (243-426)	0.55	-	-	5 (100)	-	-	-
	B		58 (53-61)		3 (60)		365 (274-1096)		-	-	5 (100)	-	-	-
	C		52 (47-53)		2 (40)		304 (213-487)		-	-	5 (100)	-	-	-
087	-	17	53 (46-65)	-	8 (47.1)	-	274 (182-700)	-	-	-	17 (100)	-	-	-
088	-	19	56 (46-63)	-	15 (79)	-	670 (335-2375)	-	76.4 (57.9-79.8)	-	19 (100)	-	-	-
303	-	19	59 (46-64)	-	17 (89.5)	-	670 (274-2558)	-	-	-	19 (100)	-	13 (12-16)	-
304	-	14	52 (50-57)	-	14 (100)	-	929 (365-1127)	-	43.8 (36.3-80.9)	-	13 (92.9)	-	-	-
305	-	15	71 (58-75)	-	8 (53.3)	-	280 (231-392)	-	-	-	-	-	-	-
306	-	10	51.5 (41-72)	-	4 (40)	-	244 (122-639)	-	-	-	-	-	13 (8-15)	-
307	A	13	68 (64-69)	0.90	10 (76.9)	1.00	30 (30-30)	1.00	-	-	13 (100)	-	5 (5-8)	0.86
	B	13	66 (66-69)		10 (76.9)		30 (30-30)		-	-	13 (100)	-	5 (5-6)	
308	-	14	66.5 (55-76)	-	7 (50)	-	1385.5 (792-1766)	-	-	-	13 (92.9)	-	-	-
310	-	20	64.5 (52-68.5)	-	11 (55)	-	1278.5 (731-1643.5)	-	-	-	-	-	-	-
314	-	68	74.5 (67-78.5)	-	34 (50)	-	400 (365.5-450.5)	-	65.2 (25.9-91.2)	-	-	-	-	-
315	-	42	60.4 (50.4-69.1)	-	-	-	749 (475-1534)	-	-	-	-	-	-	-
317	-	18	59 (54-65)	-	13 (72.2)	-	1370 (457-2832)	-	77.7 (71.4-90.2)	-	-	-	16 (14-18)	-

Study ID	Group allocation	n	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transform score, median (IQR)	Wilcoxon two sample t-test <sup>133</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>134</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for years of education differences between groups (p-value)
320	-	30	55.5 (47-63)	-	-	-	1431.5 (426-3197)	-	76.8 (62.4-92.2)	-	-	-	14 (12-16)	-
321	-	31	64 (56-67)	-	21 (67.7)	-	822 (426-1401)	-	82.6 (59-90)	-	31 (100)	-	-	-
322	-	13	69 (64-77)	-	14 (46.7)	-	974.5 (700-1918)	-	78.1 (64.2-87.8)	-	-	-	9.5 (8-14)	-
325	-	30	58.5 (53-65)	-	14 (46.7)	-	731 (365-1583)	-	54.7 (31.8-86.2)	-	30 (100)	-	-	-
326	-	29	63 (51-71)	-	14 (48.3)	-	950 (548-1972)	-	-	-	-	-	14 (12-16)	-
329	-	28	52 (47-66)	-	14 (50)	-	1126.5 (883-1568.5)	-	-	-	28 (100)	-	-	-
332	-	27	58 (53-64)	-	24 (88.9)	-	518 (274-1066)	-	-	-	27 (100)	-	-	-
333	-	-	-	-	-	-	402 (365-548)	-	-	-	26 (100)	-	-	-
335	-	26	62 (57-71)	-	14 (53.9)	-	426 (213-639)	-	87.3 (80.8-87.4)	-	26 (100)	-	12 (10-14)	-
336	-	25	62.7 (60.5-67.8)	-	-	-	1278 (475-1863)	-	-	-	-	-	-	-
337	-	25	57 (49-67)	-	14 (56)	-	1899 (840-2959)	-	89 (83-93)	-	-	-	17 (15-18)	-
338	-	24	55 (52-64.5)	-	14 (58.3)	-	11 (7-18.5)	-	-	-	24 (100)	-	-	-
340	-	23	66 (49-72)	-	-	-	670 (244-1552)	-	-	-	22 (95.7)	-	-	-
342	-	23	55 (46-60)	-	14 (60.9)	-	822 (487-1797)	-	-	-	23 (100)	-	9 (9-14)	-
346	-	23	61 (47-75)	-	-	-	97 (55-335)	-	-	-	23 (100)	-	12 (12-12)	-
348	A	11	55.4 (52.5-62.7)	1.00	9 (81.8)	0.18	719 (356-1328)	0.88	-	-	10 (90.9)	0.51	-	-
	B	9	61.4 (49.1-64.5)		9 (100)		761 (344-1185)		-	-	7 (77.8)		-	-
349	-	36	58 (50.5-65.5)	-	26 (72.2)	-	122 (91-2101)	-	-	-	36 (100)	-	-	-
351	-	20	66 (54-71)	-	13 (65)	-	305 (259-365)	-	-	-	20 (100)	-	12 (8-13)	-
352	-	20	57 (50-61)	-	13 (65)	-	2588.5 (1507.5-3623.5)	-	-	-	20 (100)	-	-	-
353	-	19	68 (59-73)	-	7 (36.8)	-	91 (91-122)	-	-	-	19 (100)	-	-	-
358	-	17	60 (53-69)	-	-	-	639 (305-1309)	-	69.8 (41.7-87.2)	-	17 (100)	-	-	-
359	-	17	63 (52-74)	-	10 (58.8)	-	1461 (731-2557)	-	74.7 (66.4-88.6)	-	-	-	-	-
360	-	17	66 (59-69)	-	12 (70.6)	-	1127 (518-2375)	-	-	-	17 (100)	-	-	-
361	-	16	60.5 (53-69)	-	11 (68.8)	-	715.5 (426-1142)	-	79 (51.2-87.2)	-	13 (100)	-	-	-

continued

TABLE 13 Between-group comparison of demographics at baseline, non-RCT data sets (continued)

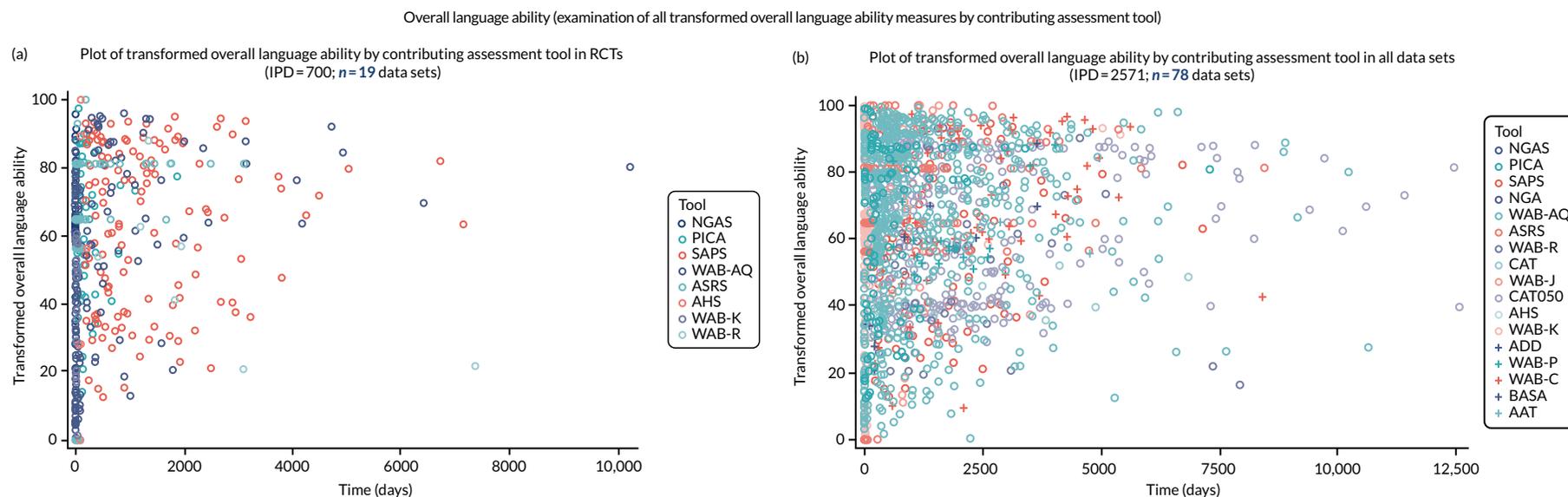
Study ID	Group allocation	n	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transform score, median (IQR)	Wilcoxon two sample t-test <sup>133</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>134</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for years of education differences between groups (p-value)
362	-	14	52 (48-55)	-	8 (57.1)	-	639.5 (274-1675)	-	-	-	14 (100)	-	-	-
364	-	16	57 (50.5-70)	-	9 (56.3)	-	1430.5 (898-2009)	-	72.9 (63.6-86.3)	-	16 (100)	-	-	-
365	-	16	58 (47.5-65.5)	-	12 (75)	-	761 (396-1643)	-	73.1 (67.9-86.8)	-	-	-	-	-
367	-	15	58 (50-63)	-	9 (60)	-	1826 (1095-3986)	-	61.7 (58.1-87)	-	15 (100)	-	12.8 (12-16)	-
369	-	10	65.5 (45-68)	-	8 (80)	-	760.5 (456-1278)	-	-	-	10 (100)	-	12 (2-12)	-
370	-	15	68 (60-78)	-	13 (86.7)	-	1095 (761-1917)	-	-	-	15 (100)	-	11.5 (9-12)	-
371	-	15	60 (51-66)	-	8 (53.3)	-	1582 (1217-2678)	-	87.8 (71.4-93.2)	-	15 (100)	-	16 (15-17)	-
372	-	15	68 (52-72)	-	10 (66.7)	-	426 (274-1248)	-	-	-	15 (100)	-	13.5 (12-14)	-
374	-	14	67.5 (61-72)	-	10 (71.4)	-	791 (456-1795)	-	94.6 (85.4-96)	-	14 (100)	-	16 (14-16)	-
375	A	8	61.5 (50.5-69.5)	0.57	-	-	898 (502-1445)	0.42	46.3 (32.3-61.6)	0.24	-	-	-	-
	B	6	67 (60-74)	-	-	-	1886.5 (274-2830)	-	56.9 (46.6-74.5)	-	-	-	-	-
377	-	14	66 (60-70)	-	-	-	1096 (1096-1826)	-	84.2 (41.4-88.5)	-	14 (100)	-	-	-
378	-	13	55 (50-63)	-	-	-	1430 (852-2191)	-	35.6 (24.9-56.2)	-	-	-	-	-
379	-	13	69 (55-73)	-	9 (69.2)	-	1644 (913-2009)	-	-	-	-	-	10 (10-11)	-
381	-	11	61 (46-66)	-	-	-	1369 (1126-2921)	-	64.9 (60.6-92.9)	-	-	-	12 (12-16)	-
394	-	12	56.5 (43.5-65.5)	-	5 (41.7)	-	1416 (685-3273)	-	69 (41.7-86.2)	-	-	-	-	-
396	-	10	54 (46-58)	-	4 (40)	-	532.5 (274-1218)	-	74 (47-92.5)	-	-	-	13 (12-15)	-
397	-	11	63 (54-66)	-	9 (81.8)	-	365 (365-1096)	-	-	-	11 (100)	-	-	-
398	-	11	56 (41-68)	-	8 (72.7)	-	1188 (670-1583)	-	-	-	11 (100)	-	11 (8-13)	-
399	-	11	73 (63-83)	-	5 (45.5)	-	91 (61-244)	-	-	-	9 (81.8)	-	12 (11-14)	-
402	-	10	69.5 (60-74)	-	4 (40)	-	1157 (639-2497)	-	-	-	10 (100)	-	12 (12-12)	-
403	-	10	57.5 (48-65)	-	7 (70)	-	639.5 (365-1096)	-	66.4 (57.2-77.4)	-	9 (90)	-	16 (16-18)	-
405	-	10	61.5 (58-70)	-	8 (80)	-	1964 (974-3075)	-	47.9 (31.8-63.5)	-	10 (100)	-	-	-
407	-	10	59 (48-64)	-	10 (100)	-	517 (365-1583)	-	-	-	9 (90)	-	10 (9-11)	-
409	-	10	58.5 (53-73)	-	4 (40)	-	1446 (668-3258)	-	68.4 (64.8-75.1)	-	-	-	-	-

Study ID	Group allocation	n	Age (years), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for age differences between groups (p-value)	Male sex, n (%)	Chi-squared test <sup>134</sup> for sex differences between groups (p-value)	Time between stroke onset and inclusion (days), median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for time differences between groups (p-value)	Aphasia severity (WAB-AQ) transform score, median (IQR)	Wilcoxon two sample t-test <sup>133</sup> for overall aphasia severity differences between groups (p-value)	Right handedness, n (%)	Chi-squared test <sup>134</sup> for handedness differences between groups (p-value)	Years of education, median (IQR)	Wilcoxon signed-rank test <sup>133</sup> for years of education differences between groups (p-value)
411	-	10	55.5 (51-59)	-	7 (70)	-	654 (426-1095)	-	-	-	-	-	-	-
412	-	10	62 (48-68)	-	4 (40)	-	1643.5 (1095-2191)	-	-	-	10 (100)	-	-	-
413	-	10	54.5 (36-75)	-	4 (40)	-	883 (426-1218)	-	-	-	10 (100)	-	-	-
414	-	10	50.5 (45-55)	-	7 (70)	-	1853 (1734-2191)	-	-	-	10 (100)	-	10.5 (9-16)	-
415	-	10	67 (61-69)	-	10 (100)	-	1159.5 (487-2375)	-	68.4 (37.6-80.4)	-	-	-	-	-
421	-	18	67 (55-75)	-	-	-	1506.5 (730-3410)	-	44.3 (26.7-86.7)	-	18 (100)	-	14 (12-16)	-
424	-	20	57.5 (46.5-63)	-	13 (65)	-	228 (137-775.5)	-	-	-	17 (85)	-	12 (12-16)	-
425	-	42	60 (50-68)	-	26 (61.9)	-	730.5 (475-1571)	-	-	-	42 (100)	-	16 (12-18)	-
462	-	36	-	-	-	-	16.5 (14-18)	-	82.9 (43.9-90.4)	-	36 (100)	-	-	-
466	-	28	62.5 (58-65)	-	28 (100)	-	49 (28-164.5)	-	-	-	28 (100)	-	-	-
470	-	14	66 (63-73)	-	7 (50)	-	943.5 (578-1339)	-	51.9 (17.4-80.3)	-	-	-	-	-
473	-	12	58 (54.5-67.5)	-	7 (58.3)	-	1217 (471.5-2571.5)	-	80.4 (73.5-93.2)	-	12 (100)	-	-	-
512	-	12	67.5 (61.5-73)	-	7 (58.3)	-	1096 (913-1644.5)	-	-	-	-	-	-	-
524	-	22	-	-	22 (100)	-	28 (21-147)	-	-	-	22 (100)	-	-	-
528	-	10	55 (48-67)	-	-	-	836.5 (517-3165)	-	81.6 (69.8-87.5)	-	-	-	16 (14-18)	-
529	-	10	48.5 (46-61)	-	6 (60)	-	1719.5 (791-2465)	-	82.1 (68-85.8)	-	10 (100)	-	12 (12-14)	-
534	-	15	73 (64-77)	-	7 (46.7)	-	1156 (669-1522)	-	46.7 (27.2-61.7)	-	-	-	9 (8-12)	-

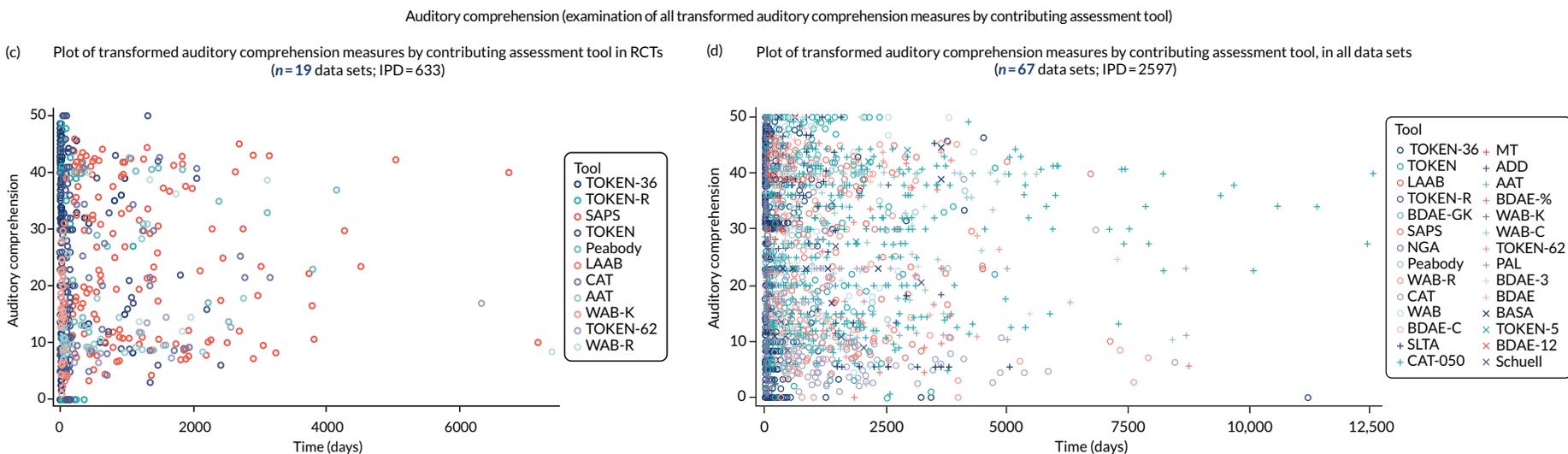
a Kruskal-Wallis test.  
Shading indicates significant results.



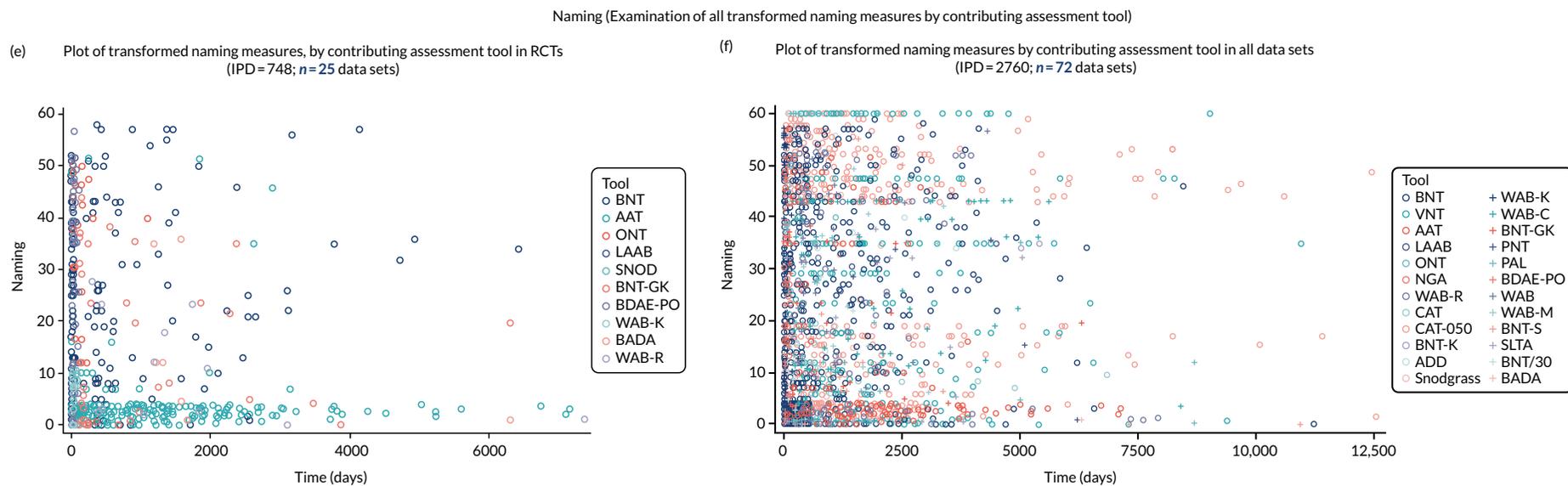
# Appendix 6 Reliability checks for the transformation algorithm



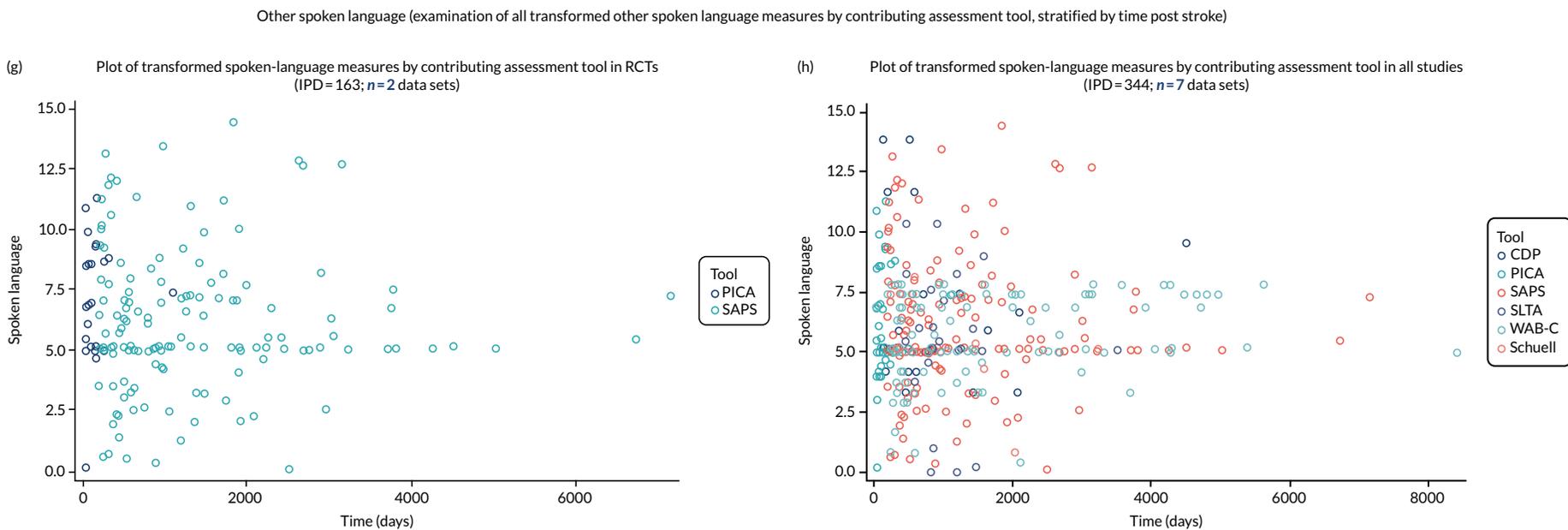
**FIGURE 27** Summary of transformed measures by contributing assessment tool. (a) Overall language ability in RCTs; (b) overall language ability in all data sets; (c) auditory comprehension in RCTs; (d) auditory comprehension in all data sets; (e) naming in RCTs; (f) naming in all data sets; (g) other spoken language in RCTs; (h) other spoken language in all data sets in RCTs; (i) reading comprehension; (j) writing; (k) functional communication: observer-rated (with activity data) in RCTs; (l) functional communication: observer-rated (with activity data) in all data sets. ADD, Afazi Dil Değerlendirme Testi; ADHD, attention deficit hyperactivity disorder; AHS, Aphasia Handicap Scale; ANELT, Amsterdam Nijmegen Everyday Language Test; ASHA, American Speech–Language–Hearing Association; ASRS, Aphasia Severity Rating Scale; BADA, Batteria per l'Analisi dei Deficit Afasici; BASA, Boston Assessment of Severe Aphasia; BDAE, Boston Diagnostic Aphasia Examination; BDAE-GK, Boston Diagnostic Aphasia Examination – Greek; BDAE-PO, Boston Diagnostic Aphasia Examination – Polish; BETA, Bateria para la Evaluación de los Trastornos Afásicos; BNT-GK, BNT – Greek; BNT-K, BNT – Korean; BNT-S, BNT – Short Form; CAL, Communicative Activity Log; FCP, Functional Communication Profile; CDP, Communication Disability Profile; CETI, Communication Effectiveness Index; NGA, Norsk Grunntest for Afasi; NGAS, Norsk Grunntest for Afasi – short; PAL, Psycholinguistic Assessment of Language; Peabody, Peabody Picture Vocabulary Test; PNT, Philadelphia Naming Test; SAPS, Sprachsystematische Aphasiescreening; Scen, Scenario Test; SLTA, Standard Language Test of Aphasia; TOMs-A, TOMs Activity; VNT, Verb Naming Test; WAB-C, WAB – Cantonese; WAB-J, WAB – Japanese; WAB-K, WAB – Korean; WAB-M, WAB – Mandarin; WAB-P, WAB – Persian; WAB-R, WAB – Revised. Reproduced with permission from Ali *et al.*<sup>118</sup> This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The figure includes minor additions and formatting changes to the original figure. (*continued*)



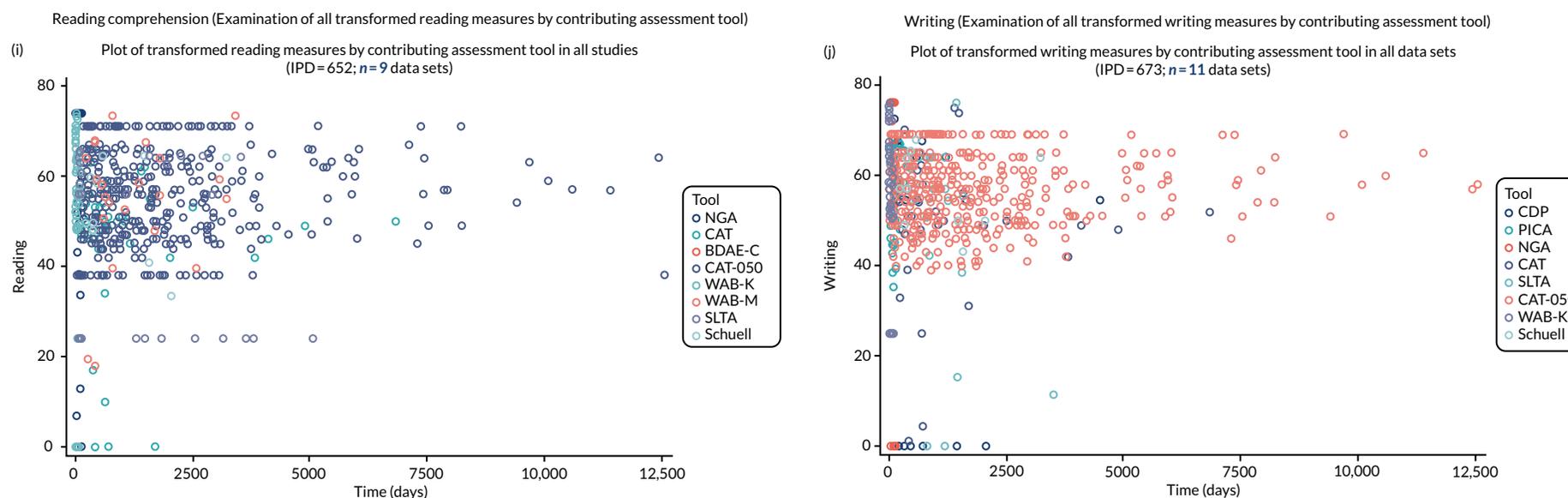
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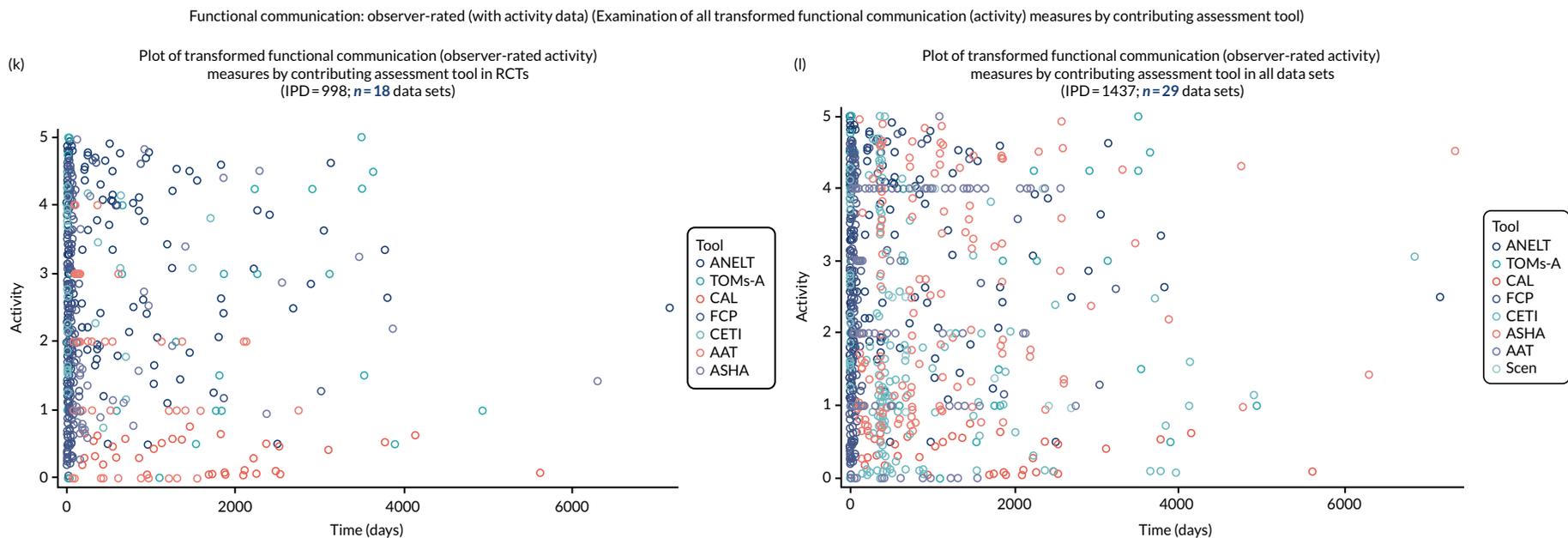
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**FIGURE 27** Summary of transformed measures by contributing assessment tool. (a) Overall language ability in RCTs; (b) overall language ability in all data sets; (c) auditory comprehension in RCTs; (d) auditory comprehension in all data sets; (e) naming in RCTs; (f) naming in all data sets; (g) other spoken language in RCTs; (h) other spoken language in all data sets; (i) reading comprehension; (j) writing; (k) functional communication: observer-rated (with activity data) in RCTs; (l) functional communication: observer-rated (with activity data) in all data sets. ADD, Afazi Dil Değerlendirme Testi; ADHD, attention deficit hyperactivity disorder; AHS, Aphasia Handicap Scale; ANELT, Amsterdam Nijmegen Everyday Language Test; ASHA, American Speech–Language–Hearing Association; ASRS, Aphasia Severity Rating Scale; BADA, Batteria per l'Analisi dei Deficit Afasici; BASA, Boston Assessment of Severe Aphasia; BDAE, Boston Diagnostic Aphasia Examination; BDAE-GK, Boston Diagnostic Aphasia Examination – Greek; BDAE-PO, Boston Diagnostic Aphasia Examination – Polish; BETA, Bateria para la Evaluación de los Trastornos Afásicos; BNT-GK, BNT – Greek; BNT-K, BNT – Korean; BNT-S, BNT – Short Form; CAL, Communicative Activity Log; FCP, Functional Communication Profile; CDP, Communication Disability Profile; CETI, Communication Effectiveness Index; NGA, Norsk Grunntest for Afasi; NGAS, Norsk Grunntest for Afasi – short; PAL, Psycholinguistic Assessment of Language; Peabody, Peabody Picture Vocabulary Test; PNT, Philadelphia Naming Test; SAPS, Sprachsystematische Aphasiescreening; Scen, Scenario Test; SLTA, Standard Language Test of Aphasia; TOMs-A, TOMs Activity; VNT, Verb Naming Test; WAB-C, WAB – Cantonese; WAB-J, WAB – Japanese; WAB-K, WAB – Korean; WAB-M, WAB – Mandarin; WAB-P, WAB – Persian; WAB-R, WAB – Revised. Reproduced with permission from Ali *et al.*<sup>118</sup> This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The figure includes minor additions and formatting changes to the original figure.

**Figure 27, parts a and b: overall language ability (examination of all transformed overall language ability measures by contributing assessment tool)**

We observed that the spread of data points overlapped, and there did not appear to be a clustering of transformed overall language ability measures that were generated from any one particular measurement tool. We therefore concluded that the transformed overall language ability values that were generated by each of the assessment tools were valid and within an expected range.

**Figure 27, parts c and d: auditory comprehension (examination of all transformed auditory comprehension measures by contributing assessment tool)**

We observed that the spread of data points overlapped, and there did not appear to be a clustering of transformed auditory comprehension measures that were generated from any one particular contributing assessment tool. We therefore concluded that the transformed auditory comprehension values that were generated by each of the assessment tools were valid and within an expected range.

**Figure 27, parts e and f: naming (examination of all transformed naming measures by contributing assessment tool)**

We observed that the spread of data points overlapped, and there did not appear to be a clustering of transformed naming measures that were generated from any one particular contributing assessment tool. We therefore concluded that the transformed naming values that were generated by each of the assessment tools were valid and within an expected range.

**Figure 27, parts g and h: other spoken language (examination of all transformed other spoken-language measures by contributing assessment tool, stratified by time post stroke)**

We observed that the spread of data points overlapped, and there did not appear to be a clustering of transformed spoken-language measures that were generated from any one particular contributing assessment tool. We therefore concluded that the transformed spoken-language values that were generated by each of the assessment tools were valid and within an expected range.

**Figure 27, part i: reading comprehension (examination of all transformed reading measures by contributing assessment tool)**

We observed that the spread of data points overlapped, and there did not appear to be a clustering of transformed reading comprehension measures that were generated from any one particular contributing assessment tool. We therefore concluded that the transformed reading comprehension values that were generated by each of the assessment tools were valid and within an expected range.

**Figure 27, part j: writing (examination of all transformed writing measures by contributing assessment tool)**

We observed that the spread of data points overlapped, and there did not appear to be a clustering of transformed writing measures that were generated from any one particular contributing assessment tool. We therefore concluded that the transformed writing values that were generated by each of the assessment tools were valid and within an expected range.

**Figure 27, parts k and l: functional communication, observer rated (with activity data) [examination of all transformed functional communication (activity) measures by contributing assessment tool]**

The spread of data points observed overlapped, and there was no indication of clustering of transformed functional communication scores (observer rated) that were generated from any one particular contributing assessment tool. We therefore concluded that the transformed functional communication values that were generated by each of the assessment tools were valid and within an expected range.



## Appendix 7 Aphasia assessment tools

TABLE 14 Aphasia assessment tools included in the RELEASE study, summary statistics, data sets, IPD, and median score and IQR

Aphasia assessment tool	Data sets reporting use of (part) measure, n	Data sets (IPD) not reporting outcome (outcome data unavailable), n (IPD)	Data sets with available data (n)	IPD available (missing)	Median score (IQR)
<b>Overall language ability</b>					
AAT overall severity score	16	15 (537)	1	12 (0)	52 (48.4–55.4)
Aphasia Severity Rating Scale	14	0 (0)	14	441 (6)	2 (1–3)
NGA	3	0 (0)	3	62 (0)	110 (64–161)
PICA	8	0 (0)	8	171 (1)	9.7 (7.9–12.0)
WAB-AQ <sup>a</sup>	35	0 (0)	35	733 (0)	69.8 (42.1–87.1)
WAB-AQ Revised	6	1 (18)	5	69 (0)	74.4 (51.9–85.2)
WAB-Korean	3	0 (0)	3	125 (3)	29.6 (11.8–64)
WAB-Persian	2	0 (0)	2	86 (0)	44.6 (26.7–74.2)
WAB-Cantonese	1	0 (0)	1	105 (0)	84 (66.4–93.1)
WAB-Japanese	1	0 (0)	1	24 (0)	81 (37–91)
ADD	1	0 (0)	1	30 (23)	95 (34–160)
CAT	8	5 (180)	3	433 (37)	57.6 (51.1–62.5)
SLTA	2	1 (36)	1	24 (0)	148 (98.5–158)
Aphasia Handicap Scale	2	0 (0)	2	39 (19)	3 (2–4)
NGA–Short	2	0 (0)	2	241 (0)	022 (6–45)
BASA	1	0 (0)	1	15 (0)	39 (30–42)
SAPS	1	0 (0)	1	133 (9)	470.5 (339–578)
<b>Auditory comprehension at baseline</b>					
AAT	16	13 (353)	3	194 (2)	51 (44–57)
BDAE	7	0 (0)	7	115 (0)	83 (36–97.5)
BAAL	2	0 (0)	2	55 (0)	7 (5–8)
NGA	3	0 (0)	3	62 (0)	46 (30–62)
PICA	8	5 (120)	3	52 (0)	11.4 (9–13.9)
WAB	22	19 (371)	3	54 (0)	181 (102–193)
WAB-Revised	6	1 (15)	5	71 (1)	9.5 (6.4–24)
WAB-Korean	3	1 (10)	2	117 (1)	91 (48–157)
WAB-Cantonese	1	0	0	105 (0)	9 (6.8–9.7)
ADD	1	0	0	53 (0)	44 (26–54)
CAT	8	2 (31)	6	576 (6)	53 (45–60)
SLTA	2	0 (0)	2	60 (0)	5 (0–33)

continued

TABLE 14 Aphasia assessment tools included in the RELEASE study, summary statistics, data sets, IPD, and median score and IQR (*continued*)

Aphasia assessment tool	Data sets reporting use of (part) measure, <i>n</i>	Data sets (IPD) not reporting outcome (outcome data unavailable), <i>n</i> (IPD)	Data sets with available data ( <i>n</i> )	IPD available (missing)	Median score (IQR)
CDP	2	1 (19)	1	6 (0)	9 (8–12)
Peabody Picture Vocabulary Test	2	0 (0)	2	33 (3)	81 (40–94)
Pizzamiglion Sentence Comprehension Test	1	0 (0)	1	25 (11)	68 (53–70)
BADA	2	1 (6)	1	12 (0)	40 (40–40)
DeRenzi and Vignolo TT/62 <sup>135</sup>	2	0 (0)	2	34 (0)	29 (15–48)
DeRenzi and Faglioni TT/36 <sup>136</sup>	10	0 (0)	10	639 (0)	12 (3.5–22)
Revised TT, Arvedson, McNeil and West/five item <sup>137</sup>	1	0 (0)	1	16 (0)	2.3 (1.3–3.6)
AAT Italian version of TT	1	0 (0)	1	11 (0)	62 (54–70)
TT-AAT <sup>a</sup>	15	0 (0)	15	505 (0)	23 (11–39)
TT/15	1	0 (0)	1	25 (0)	12.4 (11.3–13.5)
Greek version of BDAE (G-BDAE)	2	0 (0)	2	50 (0)	49.5 (36.5–57)
BASA	1	0 (0)	1	15 (0)	12 (8–14)
SAPS	1	0 (0)	1	136 (6)	263 (184–303.5)
Schuell	1	0 (0)	1	10 (0)	58.5 (46.5–68.5)
Montreal–Toulouse language assessment battery for aphasia	1	0 (0)	1	11 (0)	87 (68–100)
PAL	2	0 (0)	2	79 (5)	32 (30–32)
BDAE-3	1	0 (0)	1	29 (0)	73 (47–90)
BDAE-12	1	0 (0)	1	11 (0)	8 (7–9)
TT-AAT <i>t</i> -score	2	0 (0)	2	27 (0)	44 (34–63)
Modified Short Form of De Renzi 1978 <sup>138</sup>		0 (0)		53 (0)	2 (1–6)
<b>Naming at baseline</b>					
AAT	16	1 (11)	15	524 (14)	70 (38–97.5)
BDAE	7	7 (115)	0	0	N/A
BAAL	2	0 (0)	0	55 (0)	5 (0–10)
NGA	3	2 (23)	1	39 (0)	11 (2–31)
PICA: verbal	8	5 (120)	3	52 (0)	7 (4.8–9.4)
WAB	22	20 (381)	2	44 (0)	70 (0–85.5)
WAB-Revised	6	1 (15)	5	72 (0)	8.4 (4.2–10)
WAB-Korean	3	1 (10)	2	117 (1)	12 (0–52)
WAB-Cantonese	1	0 (0)	1	105 (0)	8 (5.5–8.7)

TABLE 14 Aphasia assessment tools included in the RELEASE study, summary statistics, data sets, IPD, and median score and IQR (continued)

Aphasia assessment tool	Data sets reporting use of (part) measure, n	Data sets (IPD) not reporting outcome (outcome data unavailable), n (IPD)	Data sets with available data (n)	IPD available (missing)	Median score (IQR)
WAB-Mandarin	1	0 (0)	1	23 (0)	50 (25–65)
ADD	1	0 (0)	1	53 (0)	12 (0–28)
CAT	8	4 (129)	4	479 (5)	58 (49–64)
SLTA	2	1 (24)	1	36 (0)	2.5 (0–6.5)
BNT/60 <sup>a</sup>	30	0 (0)	30	831 (0)	12 (1–35)
BNT Short Form	3	0 (0)	3	129 (0)	5 (1–10)
BNT/30	2	0 (0)	2	21 (0)	15 (9–22)
Philadelphia Naming Test	2	0 (0)	2	25 (0)	49 (11–70)
Snodgrass and Vanderwort <sup>139</sup>	3	0 (0)	3	80 (0)	46 (17–89)
BADA	2	1 (6)	1	12 (0)	5 (3.5–6)
BETA	1	0 (0)	1	127 (134)	0 (0–15)
Graded Naming Test	1	0 (0)	1	11 (0)	1 (0–2)
Cambridge Naming Test	1	0 (0)	1	70 (0)	41 (9–54)
Verb Naming Test	1	0 (0)	1	260 (54)	16 (9–20)
Object Naming Test	3	0 (0)	3	53 (0)	1 (0–6)
PAL	2	0 (0)	2	81 (3)	28 (22–31)
PALPA 53	1	0 (0)	1	11 (0)	14 (4–26)
Korean BNT	1	0 (0)	1	10 (0)	24.5 (8–49)
Greek BDAE	2	1 (12)	1	38 (0)	29 (6–52)
Polish BDAE	1	0 (0)	1	40 (0)	60 (6–107)
Greek BNT	1	0 (0)	1	38 (0)	5.3 (1–12.5)
<b>Other spoken language at baseline</b>					
WAB-Korean	3	2 (107)	1	21 (0)	2 (0–4)
WAB-Cantonese	1	0 (0)	1	105 (0)	15 (12–19)
SLTA	2	1 (36)	1	24 (0)	41.5 (25–45.5)
CDP	1	0 (0)	1	25 (0)	9 (6–12)
SAPS	1	0 (0)	1	139 (3)	302 (187–364)
Schuell	1	0 (0)	1	10 (0)	58.8 (56–68)
PICA <sup>a</sup>	8	6 (132)	2	40 (0)	5.1 (5–8)
Greek BDAE	2	1 (12)	1	38 (0)	16 (10–21)
<b>Reading comprehension at baseline</b>					
AAT	16	14 (493)	2	54 (2)	38 (32–47)
BDAE	7	6 (102)	1	13 (0)	0 (0–18)
NGA	3	2 (23)	1	39 (0)	16 (10–22)

continued

TABLE 14 Aphasia assessment tools included in the RELEASE study, summary statistics, data sets, IPD, and median score and IQR (*continued*)

Aphasia assessment tool	Data sets reporting use of (part) measure, <i>n</i>	Data sets (IPD) not reporting outcome (outcome data unavailable), <i>n</i> (IPD)	Data sets with available data ( <i>n</i> )	IPD available (missing)	Median score (IQR)
WAB	22	21 (412)	1	13 (0)	0 (0–0)
WAB-Korean	3	2 (31)	1	81 (16)	37 (2–74)
WAB-Mandarin	1	0 (0)	1	23 (0)	90 (75–97)
CAT <sup>a</sup>	8	5 (146)	3	460 (7)	56 (48–64)
SLTA	2	1 (24)	1	36 (0)	1 (0–4.5)
BETA	1	0 (0)	1	126 (135)	14.5 (0–29)
Schuell	1	0 (0)	1	10 (0)	65.8 (63–73)
PALPA 48	1	0 (0)	1	10 (0)	33.5 (28–37)
PALPA 31	1	0 (0)	1	11 (0)	51 (16–65)
Greek BDAE	2	1 (12)	1	38 (0)	11 (3–22)
<b>Writing at baseline</b>					
BDAE	7	6 (102)	1	13 (0)	0 (0–18)
NGA	3	2 (23)	1	39 (0)	3 (1–7)
PICA	8	5 (120)	3	51 (1)	6.9 (6–7.7)
WAB-Korean	3	2 (31)	1	71 (26)	16 (0–64)
CAT <sup>a</sup>	8	5 (146)	3	454 (13)	57 (50–64)
SLTA	2	1 (36)	1	24 (0)	33 (13–39)
CDP	1	0 (0)	1	24 (0)	2.5 (1–6)
Schuell	1	0 (0)	1	10 (0)	48.5 (44–62.5)
Greek BDAE	2	1 (12)	1	38 (0)	4 (0–9)
<b>Functional communication at baseline (observer rated)</b>					
AAT-SSC <sup>a</sup>	16	8 (147)	8	402 (4)	2 (1–4)
American Speech–Language–Hearing Association Functional Assessment of Communication Skills	3	0 (0)	3	135 (0)	5.7 (4.9–6.4)
Amsterdam–Nijmegen Everyday Language Test	7	0 (0)	7	453 (142)	1.95 (1–3.4)
Communicative Activity Log	1	0 (0)	1	10 (0)	65.6 (53–84)
Mini Communicative Activity Log	1	0 (0)	1	24 (0)	26 (15.5–31)
Communication Effectiveness Index	7	0 (0)	7	300 (0)	65 (40.3–86.2)
Communicative–Pragmatic Screening [Kommunikativ–Pragmatisches Screening (KOPS)]	1	0 (0)	1	131 (11)	230 (190.5–253.5)

TABLE 14 Aphasia assessment tools included in the RELEASE study, summary statistics, data sets, IPD, and median score and IQR (continued)

Aphasia assessment tool	Data sets reporting use of (part) measure, <i>n</i>	Data sets (IPD) not reporting outcome (outcome data unavailable), <i>n</i> (IPD)	Data sets with available data ( <i>n</i> )	IPD available (missing)	Median score (IQR)
Scenario Test (2010)	1	0 (0)	1	11 (0)	46 (33–54)
TOMs Activity	3	0 (0)	3	257 (1)	2 (1–3)
TOMs Participation	3	0 (0)	3	257 (1)	2 (1–3)
Functional Communication Profile	4	0 (0)	4	249 (5)	37.1 (19.5–54.3)
<b>Functional communication at baseline (self-rated)</b>					
Assessment for Living with Aphasia <sup>a</sup>	2	0 (0)	2	43 (2)	98.5 (88.5–111.5)
Communication Confidence Rating Scale for Aphasia	1	0 (0)	1	32 (2)	67.8 (53–74.5)
CDP Auditory comprehension	1	0 (0)	1	6 (19)	9 (8–12)
CDP Spoken language	1	0 (0)	1	25 (0)	9 (6–12)
CDP Writing	1	0 (0)	1	24 (1)	2.5 (1–6)
CDP Activity	1	0 (0)	1	25 (0)	5 (3–11)
CDP Participation	1	0 (0)	1	25 (0)	39.6 (26.6–48.4)

ADD, Afazi Dil Değerlendirme Testi; BAAL, Bateria de Avaliação de Afasias de Lisboa; BADA, Bateria per l'Analisi dei Deficit Afasici; BASA, Boston Assessment of Severe Aphasia; BDAE, Boston Diagnostic Aphasia Examination; BETA, Bateria para la Evaluación de los Trastornos Afásicos; CDP, Communication Disability Profile; N/A, not available; NGA, Norsk Grunntest for Afasi; PAL, Psycholinguistic Assessment of Language; PALPA, Psycholinguistic Assessments of Language Processing in Aphasia; SAPS, Sprachsystematische Aphasiescreening; SLTA, Standard Language Test of Aphasia.

a Anchor measure.



## Appendix 8 Relationships between demography and language domains

TABLE 15 Univariable and multivariable relationships to language domains and *p*-values

Language domain	IPD (n)	Univariable (p-value)	Bivariable (including baseline)	Multivariable <sup>a</sup> (p-value)	Multivariable (p-value)
<b>Overall language ability by variable</b>		<b>N = 482</b>		<b>N = 482</b>	<b>N = 264</b>
Baseline score	482	< 0.0001	-	< 0.0001	< 0.0001
Sex	481	0.19	0.12	0.17	0.018
Hemisphere <sup>b</sup>	334	0.14	0.43	-	0.89
Type	482	0.26	0.66	0.95	0.72
Handedness	274	0.45	0.46	-	0.41
Language of data collection	482	0.28	0.021	0.094	< 0.0001
Age (grouped) (years)	482	0.86	0.27	0.21	0.32
Time since stroke (grouped)	482	0.017	0.083	0.39	0.56
<b>Auditory comprehension by variable</b>		<b>N = 550</b>		<b>N = 522</b>	<b>N = 492</b>
Baseline score	550	< 0.0001	-	< 0.0001	< 0.0001
Sex	540	0.32	0.19	0.35	0.36
Hemisphere <sup>b</sup>	509	0.13	0.13	-	0.08
Type	536	0.34	0.44	0.41	0.78
Handedness	536	0.26	0.40	0.47	0.25
Language of data collection	550	0.03	0.12	0.33	0.55
Age (years)	540	0.003	0.002	-	-
Age (four groups) (years)	540	0.0008	0.0004	0.002	0.003
Time since stroke (grouped)	540	0.20	0.20	0.33	0.26
<b>Naming by variable</b>		<b>N = 385</b>		<b>N = 381</b>	<b>N = 316</b>
Baseline score	385	0.0098	-	0.026	0.0052
Sex	385	0.80	0.75	0.87	0.74
Hemisphere <sup>b</sup>	355	0.32	0.33	-	0.30
Type <sup>c</sup>	381	0.49	0.57	0.83	0.85
Handedness	333	0.96	0.99	-	0.86
Language	385	0.0005	0.0027	0.012	0.024
Age (years)	385	0.011	0.011	-	-
Age (four groups) (years)	385	0.036	0.054	0.074	0.18
Time since stroke (grouped)	385	0.095	0.11	0.19	0.19

continued

TABLE 15 Univariable and multivariable relationships to language domains and p-values (continued)

Language domain	IPD (n)	Univariable (p-value)	Bivariable (including baseline)	Multivariable <sup>a</sup> (p-value)	Multivariable (p-value)
<b>Other spoken language variable</b>	<b>N = 231</b>				<b>N = 215<sup>d</sup></b>
Baseline score		0.36	-	-	0.20
Sex	231	0.93	-	-	0.73
Hemisphere <sup>b</sup>	226	0.79	-	-	0.81
Type	231	0.56	-	-	0.41
Handedness	225	0.47	-	-	0.40
Language	231	0.01	-	-	0.53
Age (years)	231	0.63	-	-	-
Age (grouped) (years)	231	0.26	-	-	0.02
Time since stroke	231	0.04	-	-	-
Time since stroke (grouped)	231	0.006	-	-	0.01
<b>Reading comprehension by variable</b>	<b>N = 88</b>		<b>Bivariable (including baseline)<sup>d</sup></b>	<b>Multivariable (p-value) (N = 88)<sup>d,e</sup></b>	<b>Multivariable (p-value) (N = 75)<sup>e,f</sup></b>
Baseline score	88	0.0049 <sup>a</sup>	-	0.0005	0.0004
Sex	88	0.50 <sup>a</sup>	0.67	0.96	0.98
Hemisphere <sup>b</sup>	76	0.81 <sup>a</sup>	0.40	-	-
Type	88	1.00 <sup>a</sup>	0.75	0.88	0.98
Handedness	76	0.70 <sup>a</sup>	0.74	-	0.68
Language	88	0.89 <sup>a</sup>	0.45	0.52	0.70
Age (years)	88	0.0027 <sup>a</sup>	0.0009	-	-
Age (grouped) (years)	88	0.013 <sup>a</sup>	0.001	0.002	0.0094
Time since stroke	88	0.40 <sup>a</sup>	0.43	-	-
Time since stroke (grouped)	88	0.15 <sup>a</sup>	0.12	0.21	0.36
<b>Writing by variable</b>	<b>N = 47</b>				<b>Multivariable<sup>d</sup> (p-value)</b>
Baseline score	47	0.39	-	-	0.65
Sex	47	0.53	-	-	0.77
Hemisphere <sup>b</sup>	36	0.081 <sup>a</sup>	-	-	-
Type	47	All unclassified	-	-	-
Handedness	35	All right	-	-	-
Language	47	All English	-	-	-
Age (years)	47	0.21	-	-	-
Age (grouped) (years)	47	0.68	-	-	0.74
Time since stroke	47	< 0.0001 <sup>a</sup>	-	-	-
Time since stroke (grouped)	47	0.032 <sup>a</sup>	-	-	0.027

TABLE 15 Univariable and multivariable relationships to language domains and *p*-values (continued)

Language domain	IPD (n)	Univariable (p-value)	Bivariable (including baseline)	Multivariable <sup>a</sup> (p-value)	Multivariable (p-value)
<b>Functional communication (observer rated)</b>	<b>N = 544</b>			<b>Multivariable (p-value) (N = 529)<sup>f</sup></b>	<b>N = 319</b>
Baseline score	544	< 0.0001	-	< 0.0001	< 0.0001
Sex	544	0.039	0.0046	0.011	0.021
Hemisphere <sup>b</sup>	408	0.59	0.55	-	0.34
Type	540	0.47	0.39	0.12	0.091
Handedness	349	0.56	0.74	-	0.70
Language	544	0.47	0.71	0.65	0.73
Age (years)	544	0.10	0.061	-	-
Age (grouped) (years)	544	0.56	0.27	0.28	0.038
Time since stroke	533	0.40	0.55	-	-
Time since stroke (grouped)	533	0.0009	0.0024	0.18	0.54

a Excluding hemisphere and handedness.  
b Excluding IPD with bilateral strokes (overall language ability, *n* = 4; auditory comprehension, *n* = 5; naming, *n* = 1; other spoken language, *n* = 5; reading comprehension, *n* = 1; writing, *n* = 1; and functional communication, *n* = 4).  
c Excluding one subarachnoid haemorrhage.  
d The estimated G matrix is not positive definite.  
e Not including study as a random effect (i.e. no differences between the studies have been included).  
f Excluding hemisphere and including handedness.



## Appendix 9 Functional communication (observer-rated) data with participation data

TABLE 16 Predictors of language recovery following aphasia after stroke: multivariable estimates of means (95% CIs), RCTs and all data sets for functional communication (observer rated, inclusive of TOMs participation data)

Parameter	RCT data only			All data		
	RCTs only (n)	IPD (n)	Estimate of mean <sup>a</sup> (95% CIs)	All data sets (n)	IPD (n)	Estimate of mean <sup>a</sup> (95% CIs)
<b>Sex</b>						
Female	14	237	0.71 (0.44 to 0.98)	18	275	0.70 (0.41 to 0.99)
Male	14	296	0.55 (0.28 to 0.81)	19	372	0.58 (0.30 to 0.86)
<b>Age (years)</b>						
< 55	14	147	0.74 (0.46 to 1.03)	19	181	0.72 (0.43 to 1.02)
56–65	13	145	0.66 (0.37 to 0.94)	18	170	0.66 (0.36 to 0.96)
66–75	14	122	0.50 (0.21 to 0.80)	18	148	0.53 (0.22 to 0.84)
> 75	12	119	0.62 (0.31 to 0.92)	15	148	0.65 (0.33 to 0.96)
<b>Time since stroke</b>						
0–1 month	6	232	1.07 (0.73 to 1.41)	7	277	1.07 (0.71 to 1.42)
1–3 months	5	68	0.84 (0.48 to 1.20)	6	70	0.87 (0.48 to 1.25)
3–6 months	4	63	0.35 (–0.13 to 0.82)	5	63	0.35 (–0.13 to 0.83)
> 6 months	7	170	0.26 (–0.06 to 0.58)	11	237	0.28 (–0.01 to 0.56)
			Random (no)	5	115	0.64 (0.18 to 1.10)
			Random (yes)	14	532	0.64 (0.39 to 0.90)

a As measured on the AAT SSC (0 minimum to 5 maximum).

Shading indicates evidence of positive (significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group /on that measure.

TABLE 17 Goodness of fit to baseline, sex, age and time; functional communication (observer rated), including participation data from the TOMs

Effect	RCT data only				All data			
	Number DF	Denominator DF	F-value	p-value	Number DF	Denominator DF	F-value	p-value
<b>Frequency of SLT</b>								
Baseline score	1	499	34.78	< 0.0001	1	563	36.18	< 0.0001
Sex	1	499	4.18	0.042	1	563	4.13	0.043
Age group	3	499	0.97	0.41	3	563	0.74	0.53
Time since stroke group	3	499	4.72	0.0029	3	563	4.56	0.0036
Randomisation	–	–	–	–	1	563	0.01	0.94
Frequency group	5	499	1.05	0.39	1	563	1.14	0.34

continued

TABLE 17 Goodness of fit to baseline, sex, age and time; functional communication (observer rated), including participation data from the TOMs (continued)

Effect	RCT data only				All data			
	Number DF	Denominator DF	F-value	p-value	Number DF	Denominator DF	F-value	p-value
<b>Duration of SLT</b>								
Baseline score	1	448	41.68	< 0.0001	1	512	43.99	< 0.0001
Sex	1	448	4.28	0.039	1	512	4.26	0.04
Age group	3	448	0.91	0.43	3	512	0.70	0.55
Time since stroke group	3	448	5.03	0.0019	3	512	4.17	0.0062
Randomisation	-	-	-	-	1	512	0.34	0.56
Duration group	5	448	1.15	0.33	5	512	1.52	0.18
<b>Intensity of SLT</b>								
Baseline score	1	506	39.91	< 0.0001	1	616	55.11	< 0.0001
Sex	1	506	3.72	0.055	1	616	2.28	0.13
Age group	3	506	1.42	0.24	3	616	1.18	0.32
Time since stroke group	3	506	4.50	0.0039	3	616	3.94	0.0084
Randomisation	-	-	-	-	1	616	0.01	0.91
Intensity group	5	506	1.16	0.33	5	616	1.26	0.28
<b>Dosage of SLT</b>								
Baseline score	1	497	40.35	< 0.0001	1	560	41.50	< 0.0001
Sex	1	497	5.70	0.017	1	560	5.73	0.017
Age group	3	497	0.96	0.41	3	560	0.78	0.51
Time since stroke group	3	497	4.11	0.0067	3	560	3.95	0.0083
Randomisation	-	-	-	-	1	560	0.00	0.95
Dosage group	5	497	2.74	0.019	5	560	3.11	0.0089
<b>Home practice of SLT</b>								
Baseline score	1	431	38.38	< 0.0001	1	531	52.96	< 0.0001
Sex	1	431	2.83	0.093	1	531	1.61	0.21
Age group	3	431	1.92	0.13	3	531	1.63	0.18
Time since stroke group	3	431	4.24	0.0057	3	531	4.52	0.0039
Randomisation	-	-	-	-	1	531	0.02	0.90
Home practice	1	431	0.40	0.53	1	531	0.41	0.52
<b>SLT target</b>								
Baseline score	1	345	28.00	< 0.0001	1	409	29.79	< 0.0001
Sex	1	345	4.90	0.028	1	409	5.08	0.025
Age group	3	345	1.68	0.17	3	409	1.44	0.23
Time since stroke group	3	345	2.34	0.07	3	409	1.92	0.13
Randomisation	-	-	-	-	1	409	0.01	0.91
SLT target	3	345	0.73	0.53	4	409	0.70	0.59

TABLE 17 Goodness of fit to baseline, sex, age and time; functional communication (observer rated), including participation data from the TOMs (continued)

Effect	RCT data only				All data			
	Number DF	Denominator DF	F-value	p-value	Number DF	Denominator DF	F-value	p-value
<b>SLT theoretical approach</b>								
Baseline score	1	234	17.09	< 0.0001	1	292	16.26	< 0.0001
Sex	1	234	3.93	0.049	1	292	3.94	0.048
Age group	3	234	2.19	0.09	3	292	2.25	0.083
Time since stroke group	3	234	2.16	0.09	3	292	3.15	0.025
Randomisation	-	-	-	-	1	292	0.04	0.84
Theoretical approach	6	234	0.75	0.61	6	292	1.94	0.075
<b>Expertise-non-professional</b>								
Baseline score	1	509	39.51	< 0.0001	1	619	53.99	< 0.0001
Sex	1	509	3.71	0.055	1	619	2.38	0.12
Age group	3	509	1.42	0.24	3	619	1.22	0.30
Time since stroke group	3	509	3.88	0.0092	3	619	4.56	0.0036
Randomisation	-	-	-	-	1	619	0.00	0.96
Expertise-professional	1	509	2.96	0.086	1	619	3.58	0.059
Expertise-non-professional	1	509	1.56	0.21	1	619	1.64	0.20
<b>Context of therapy</b>								
Baseline score	1	509	38.36	< 0.0001	1	619	52.61	< 0.0001
Sex	1	509	3.67	0.056	1	619	2.42	0.12
Age group	3	509	1.27	0.28	3	619	1.09	0.35
Time since stroke group	3	509	5.84	0.0006	3	619	6.39	0.0003
Randomisation	-	-	-	-	1	619	0.01	0.94
Inpatient	1	509	1.43	0.23	1	619	2.26	0.13
Outpatient	1	509	2.08	0.15	1	619	2.25	0.13
<b>Mode of therapy</b>								
Baseline score	1	508	39.41	< 0.0001	1	618	54.99	< 0.0001
Sex	1	508	3.75	0.05	1	618	2.44	0.12
Age group	3	508	1.52	0.21	3	618	1.29	0.28
Time since stroke group	3	508	2.59	0.05	3	618	2.85	0.037
Randomisation	-	-	-	-	1	618	0.02	0.88
Mode: face to face	1	508	3.48	0.063	1	618	3.34	0.068
Mode: computer	1	508	0.57	0.45	1	618	1.17	0.28

continued

TABLE 17 Goodness of fit to baseline, sex, age and time; functional communication (observer rated), including participation data from the TOMs (continued)

Effect	RCT data only				All data			
	Number DF	Denominator DF	F-value	p-value	Number DF	Denominator DF	F-value	p-value
<b>Functional relevance</b>								
Baseline score	1	422	39.28	< 0.0001	1	532	54.02	< 0.0001
Sex	1	422	3.02	0.083	1	532	1.84	0.18
Age group	3	422	2.05	0.11	3	532	1.63	0.18
Time since stroke group	3	422	3.25	0.022	3	532	3.92	0.0087
Randomisation	-	-	-	-	1	532	0.06	0.81
Functional relevance	1	422	0.00	1.00	1	532	0.35	0.56
<b>Level of difficulty</b>								
Baseline score	1	431	38.43	< 0.0001	1	541	54.16	< 0.0001
Sex	1	431	2.87	0.091	1	541	1.74	0.19
Age group	3	431	1.89	0.13	3	541	1.51	0.21
Time since stroke group	3	431	4.20	0.006	3	541	4.73	0.0029
Randomisation	-	-	-	-	1	541	0.06	0.81
Level of difficulty	1	431	0.35	0.55	1	541	0.33	0.56
DF, degrees of freedom.								

TABLE 18 Increase in language performance score by unit increase in SLT regimen

Functional communication including participation data from the TOMs	Estimate, slope (SE)	Intercept (SE)
<b>Frequency of SLT</b>		
Functional communication (observer rated)	0.05 (0.02)	0.34 (0.22)
<b>Duration</b>		
Functional communication (observer rated)	0.005 (0.01)	0.44 (0.22)
<b>Intensity</b>		
Functional communication (observer rated)	0.01 (0.01)	0.39 (0.23)
<b>Dosage</b>		
Functional communication (observer rated)	-0.001 (0.01)	0.52 (0.23)
SE, standard error.		

## Appendix 10 Risk of bias

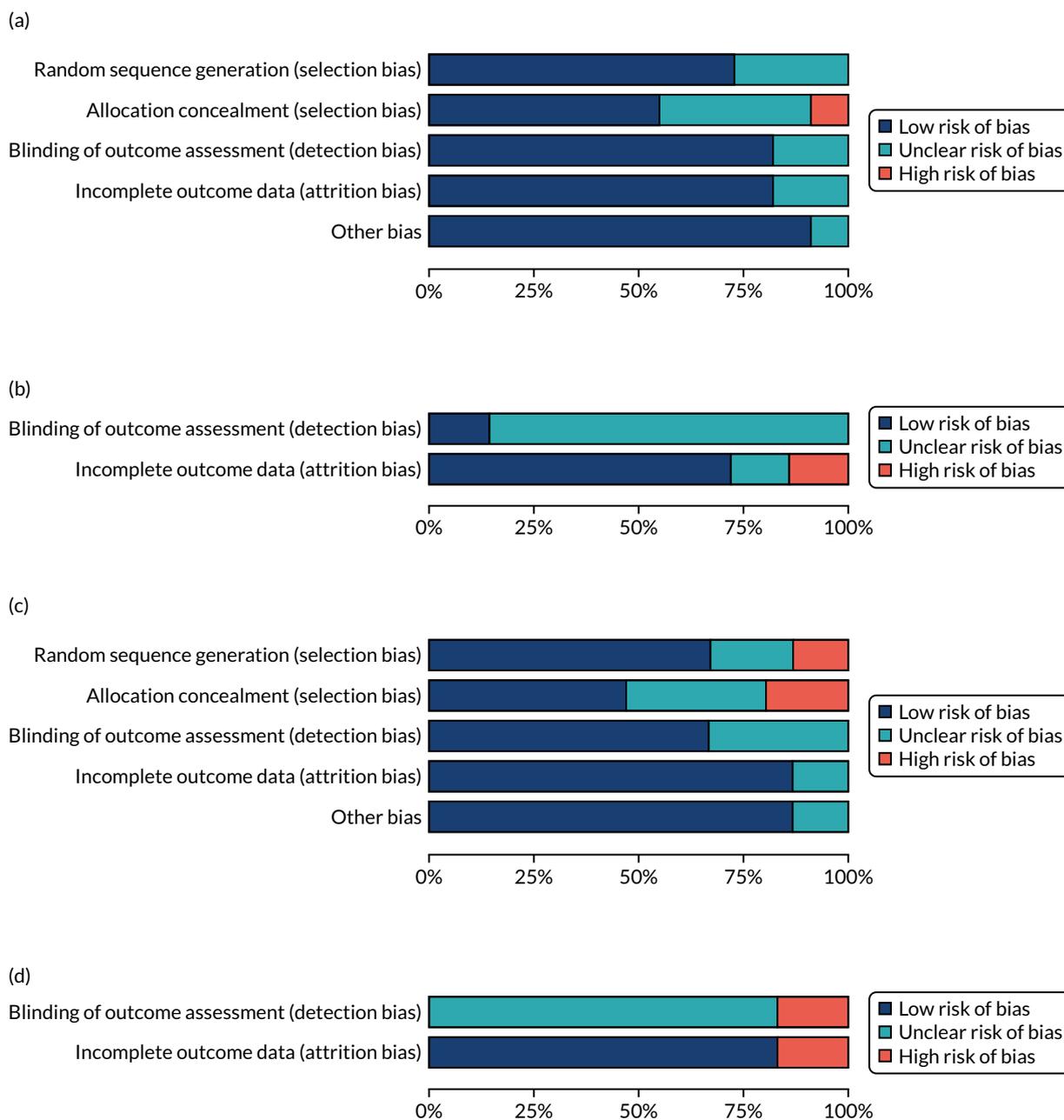


FIGURE 28 Risk of bias. (a) Overall language ability and risk of bias;  $n = 11$  RCT data sets; (b) overall language ability and risk of bias;  $n = 7$  non-RCT data sets; (c) auditory comprehension and risk of bias;  $n = 15$  RCT data sets; (d) auditory comprehension and risk of bias;  $n = 6$  non-RCT data sets; (e) naming and risk of bias;  $n = 13$  RCT data sets; (f) naming and risk of bias;  $n = 8$  non-RCT data sets; (g) other spoken language and risk of bias;  $n = 3$  RCT data sets; (h) other spoken language and risk of bias;  $n = 3$  non-RCT data sets; (i) reading and risk of bias;  $n = 4$  non-RCT data sets; (j) writing and risk of bias;  $n = 3$  RCT data sets (no non-RCT writing outcomes were available); (k) functional communication (observer rated) and risk of bias;  $n = 14$  RCT data sets; and (l) functional communication (observer rated) and risk of bias;  $n = 5$  non-RCT data sets. (continued)

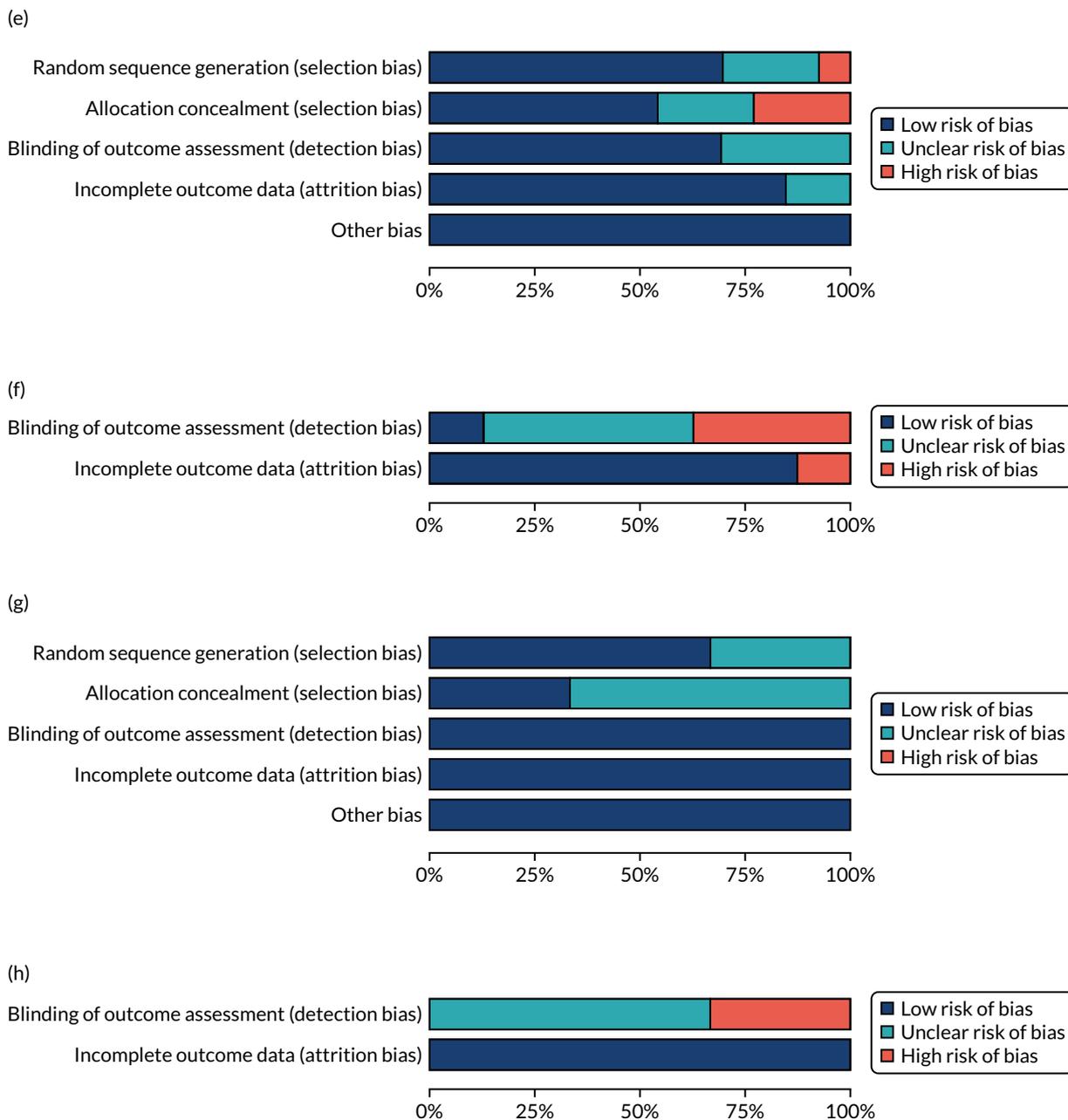


FIGURE 28 Risk of bias. (a) Overall language ability and risk of bias;  $n = 11$  RCT data sets; (b) overall language ability and risk of bias;  $n = 7$  non-RCT data sets; (c) auditory comprehension and risk of bias;  $n = 15$  RCT data sets; (d) auditory comprehension and risk of bias;  $n = 6$  non-RCT data sets; (e) naming and risk of bias;  $n = 13$  RCT data sets; (f) naming and risk of bias;  $n = 8$  non-RCT data sets; (g) other spoken language and risk of bias;  $n = 3$  RCT data sets; (h) other spoken language and risk of bias;  $n = 3$  non-RCT data sets; (i) reading and risk of bias;  $n = 4$  non-RCT data sets; (j) writing and risk of bias;  $n = 3$  RCT data sets (no non-RCT writing outcomes were available); (k) functional communication (observer rated) and risk of bias;  $n = 14$  RCT data sets; and (l) functional communication (observer rated) and risk of bias;  $n = 5$  non-RCT data sets. (continued)

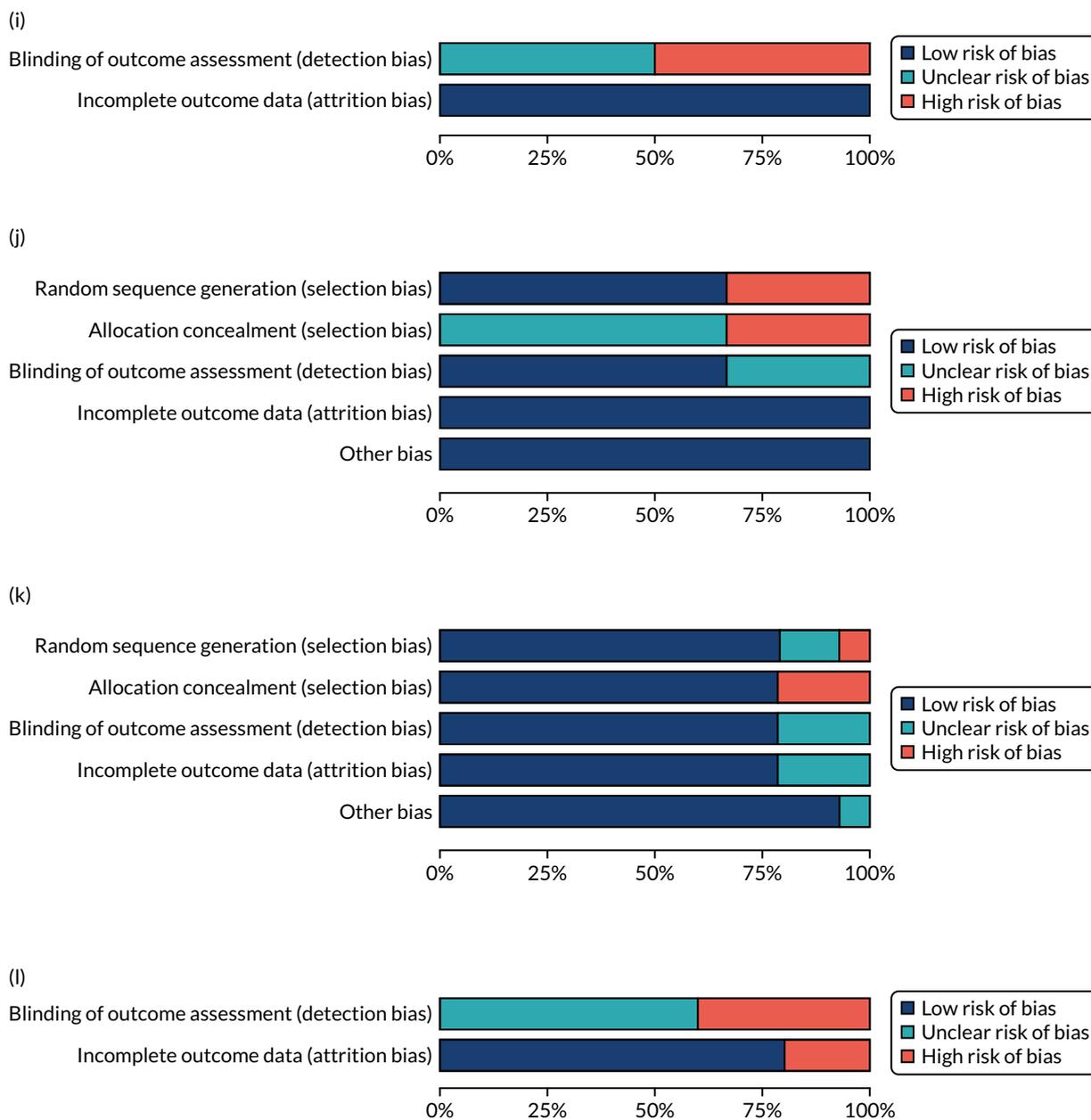
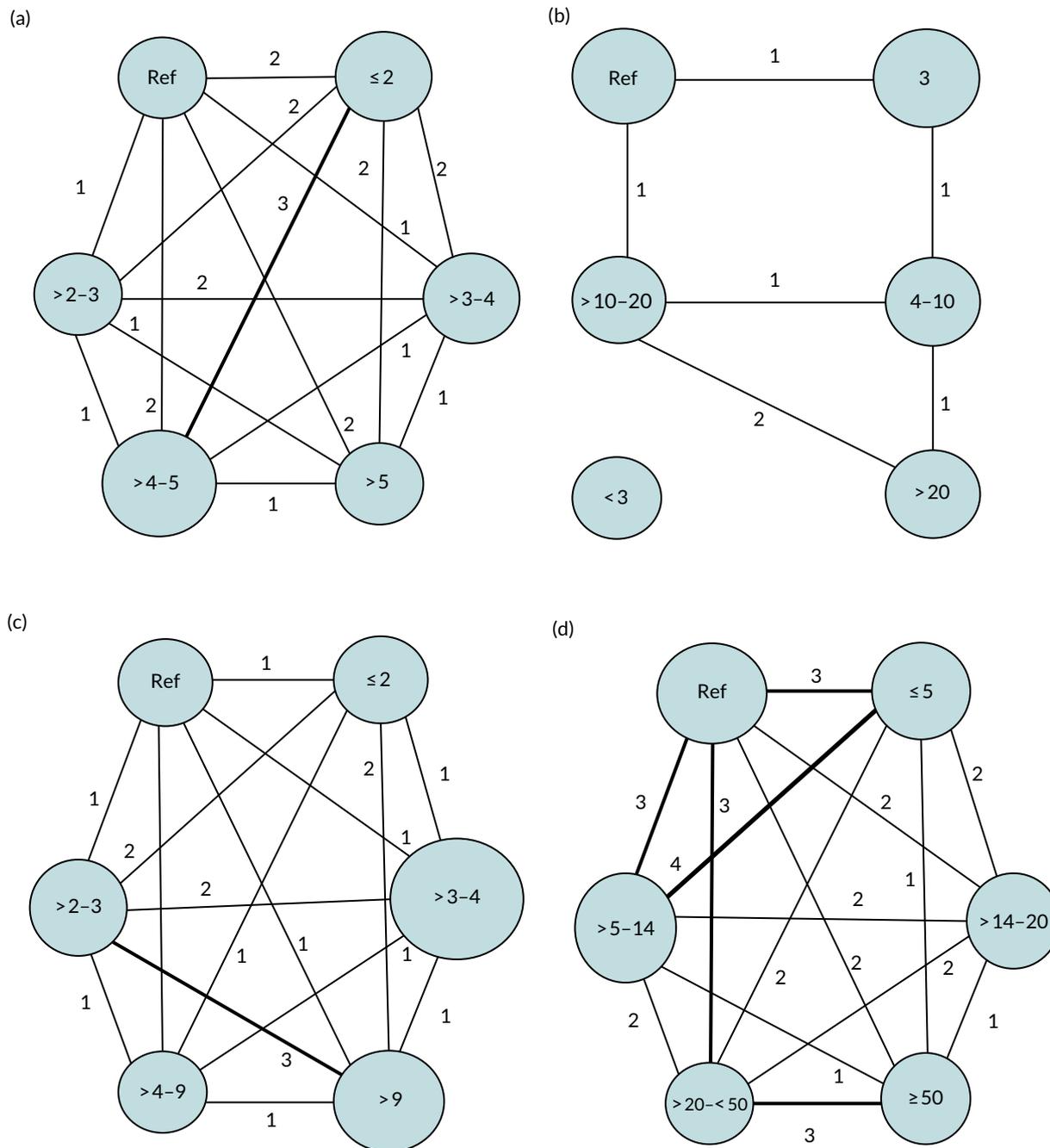


FIGURE 28 Risk of bias. (a) Overall language ability and risk of bias;  $n = 11$  RCT data sets; (b) overall language ability and risk of bias;  $n = 7$  non-RCT data sets; (c) auditory comprehension and risk of bias;  $n = 15$  RCT data sets; (d) auditory comprehension and risk of bias;  $n = 6$  non-RCT data sets; (e) naming and risk of bias;  $n = 13$  RCT data sets; (f) naming and risk of bias;  $n = 8$  non-RCT data sets; (g) other spoken language and risk of bias;  $n = 3$  RCT data sets; (h) other spoken language and risk of bias;  $n = 3$  non-RCT data sets; (i) reading and risk of bias;  $n = 4$  non-RCT data sets; (j) writing and risk of bias;  $n = 3$  RCT data sets (no non-RCT writing outcomes were available); (k) functional communication (observer rated) and risk of bias;  $n = 14$  RCT data sets; and (l) functional communication (observer rated) and risk of bias;  $n = 5$  non-RCT data sets.



## Appendix 11 Network meta-analysis geometry for overall language ability



**FIGURE 29** Network meta-analysis direct and indirect comparisons: overall language ability network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) therapy approach; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of SLT provider; (i) mode of SLT delivery; (j) context of delivery; (k) SLT tailored; (l) SLT tailored by difficulty; (m) SLT tailored by functional relevance; and (n) SLT home practice. CIAT, constraint-induced aphasia therapy; Ref, reference. (continued)

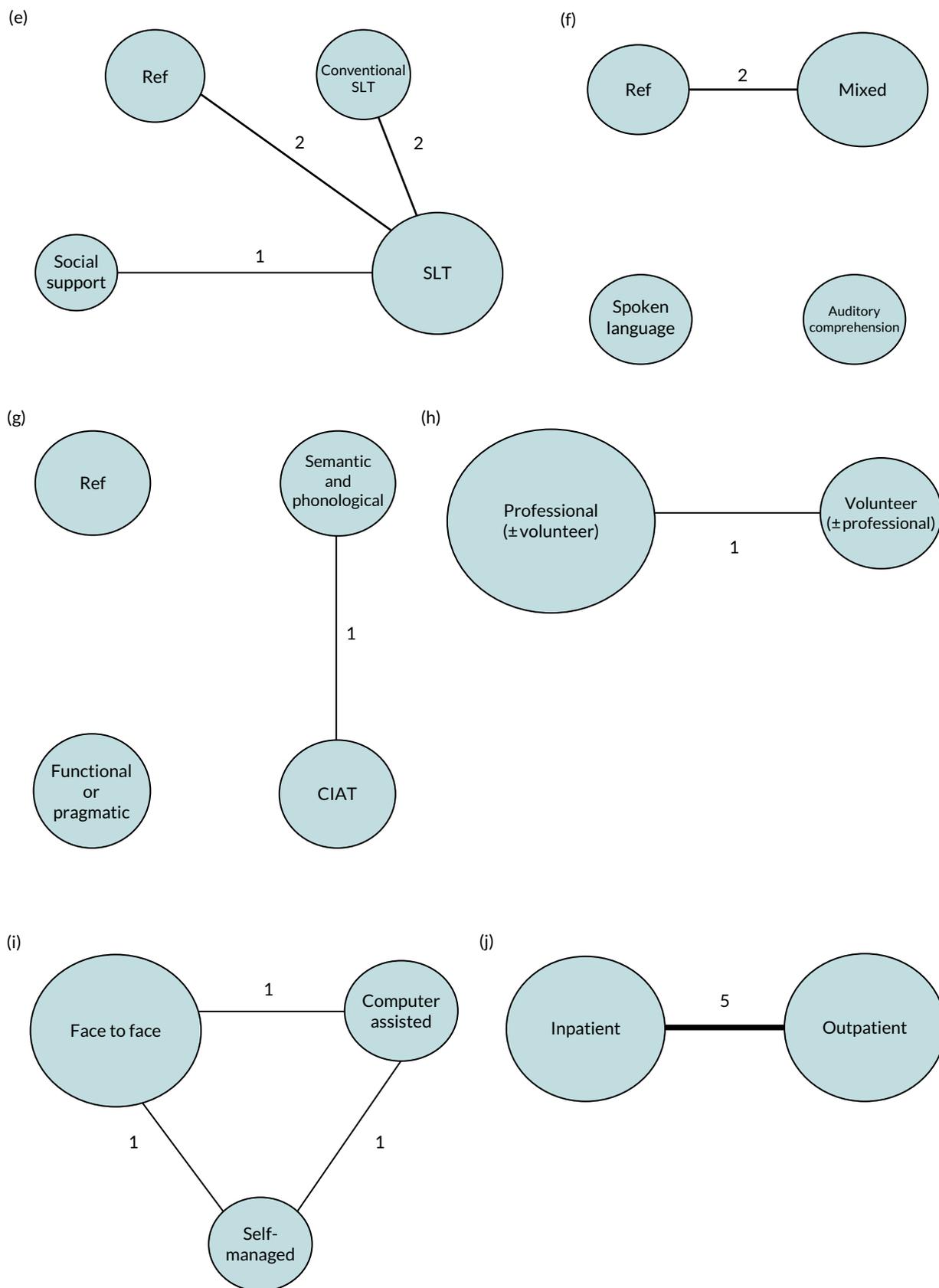


FIGURE 29 Network meta-analysis direct and indirect comparisons: overall language ability network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) therapy approach; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of SLT provider; (i) mode of SLT delivery; (j) context of delivery; (k) SLT tailored; (l) SLT tailored by difficulty; (m) SLT tailored by functional relevance; and (n) SLT home practice. CIAT, constraint-induced aphasia therapy; Ref, reference. (continued)

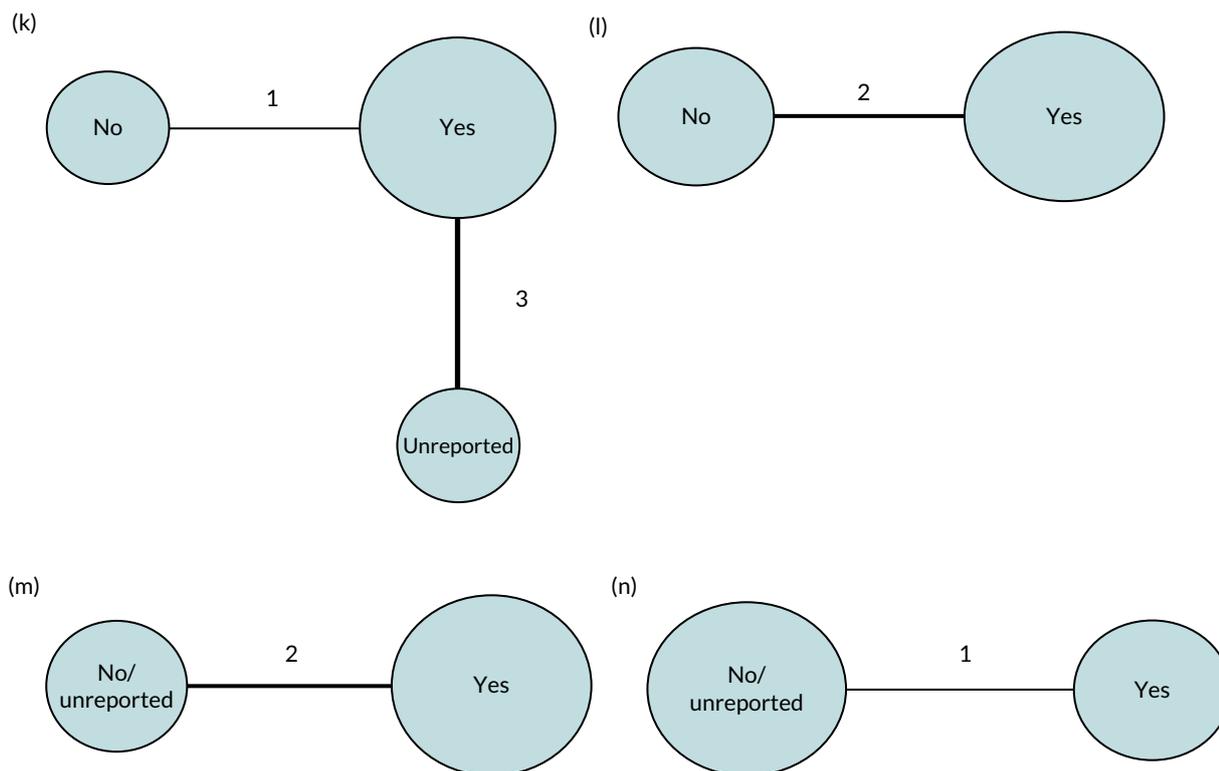
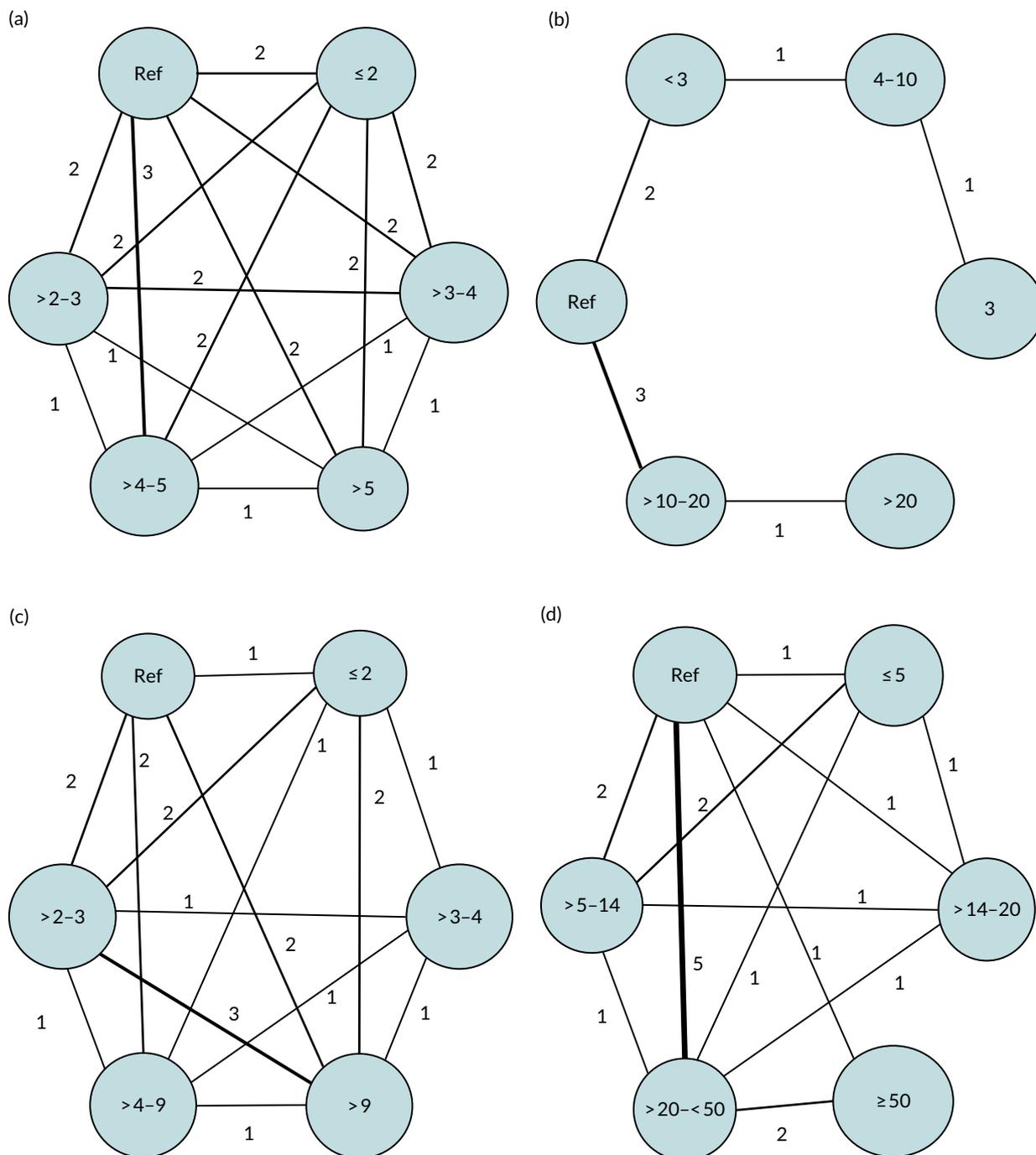


FIGURE 29 Network meta-analysis direct and indirect comparisons: overall language ability network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) therapy approach; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of SLT provider; (i) mode of SLT delivery; (j) context of delivery; (k) SLT tailored; (l) SLT tailored by difficulty; (m) SLT tailored by functional relevance; and (n) SLT home practice. CIAT, constraint-induced aphasia therapy; Ref, reference.

The network meta-analyses presented are based on the availability of IPD from RCT participants, the frequency of SLT per week and overall language ability.



## Appendix 12 Network meta-analysis geometry for auditory comprehension



**FIGURE 30** Network meta-analysis direct and indirect comparisons: auditory comprehension network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT approach by role; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) tailored SLT; (l) SLT tailored by difficulty; (m) SLT tailored by functional relevance; and (n) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference. (continued)

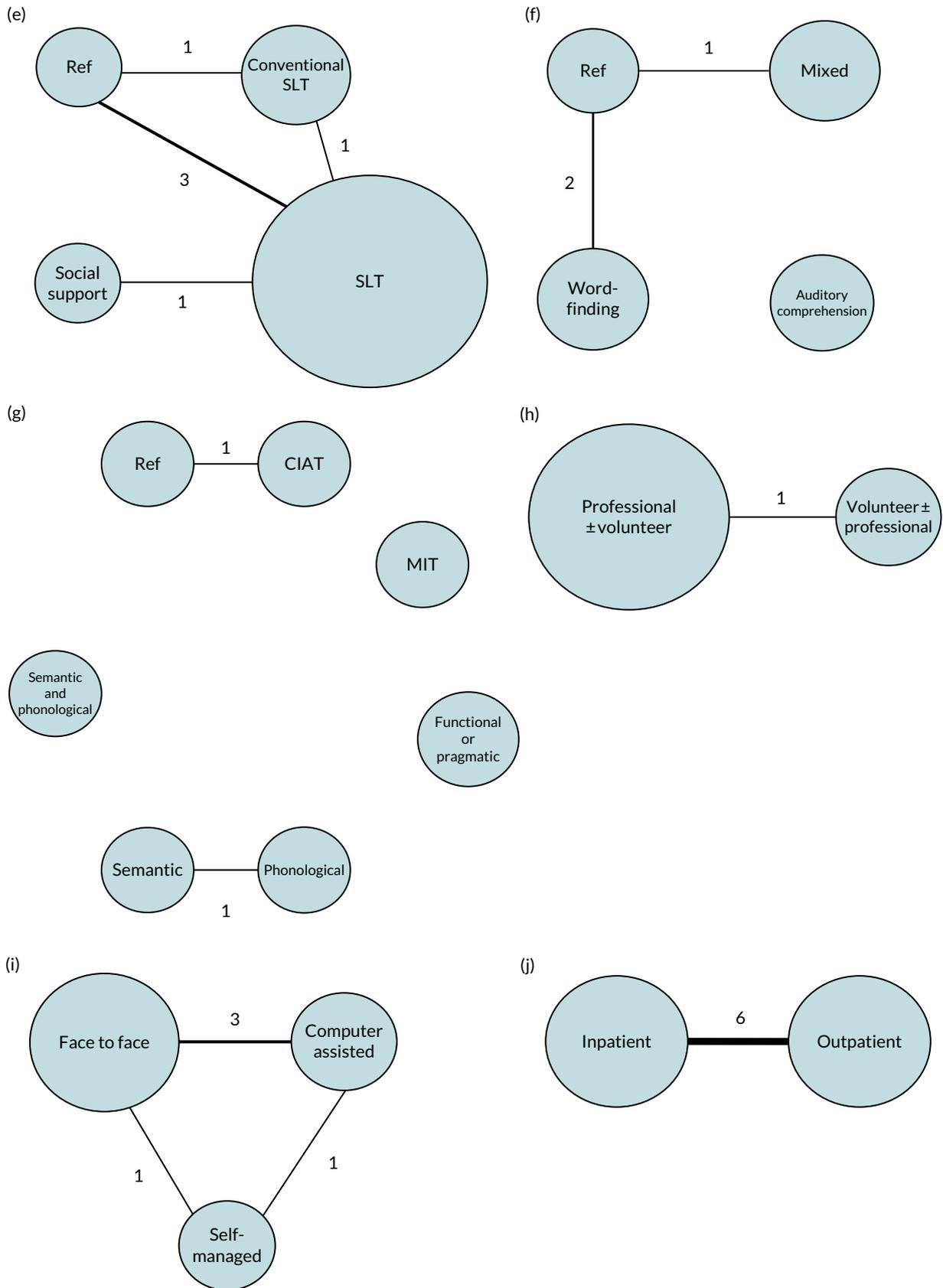


FIGURE 30 Network meta-analysis direct and indirect comparisons: auditory comprehension network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT approach by role; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) tailored SLT; (l) SLT tailored by difficulty; (m) SLT tailored by functional relevance; and (n) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference. (continued)

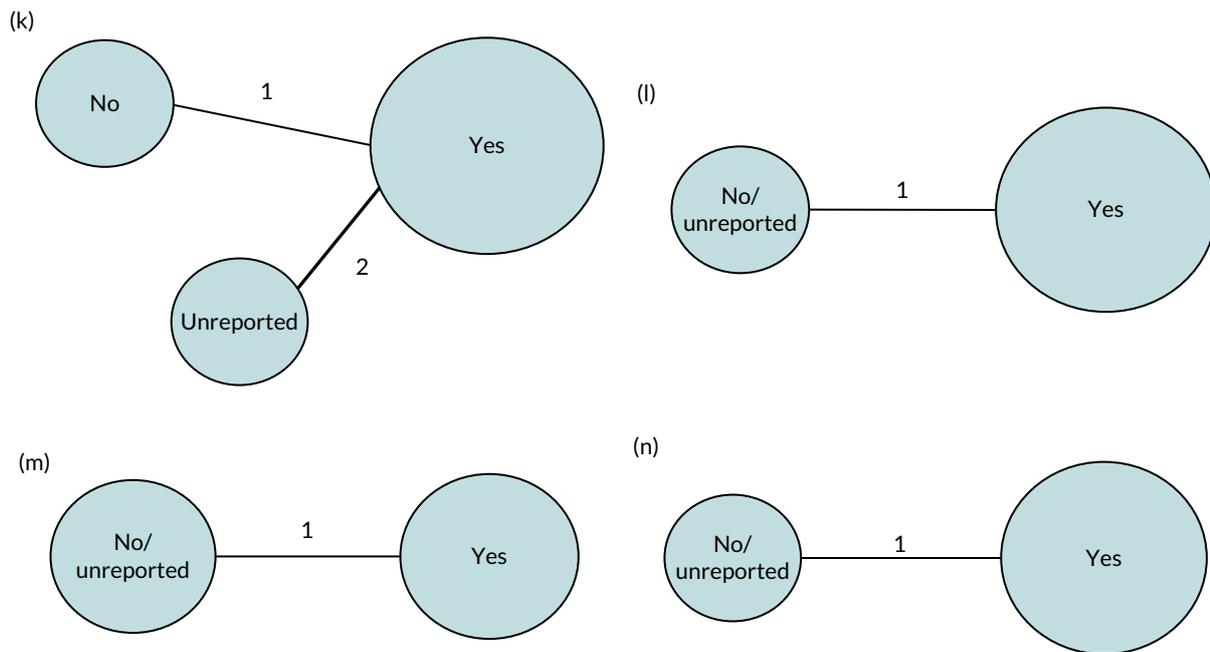
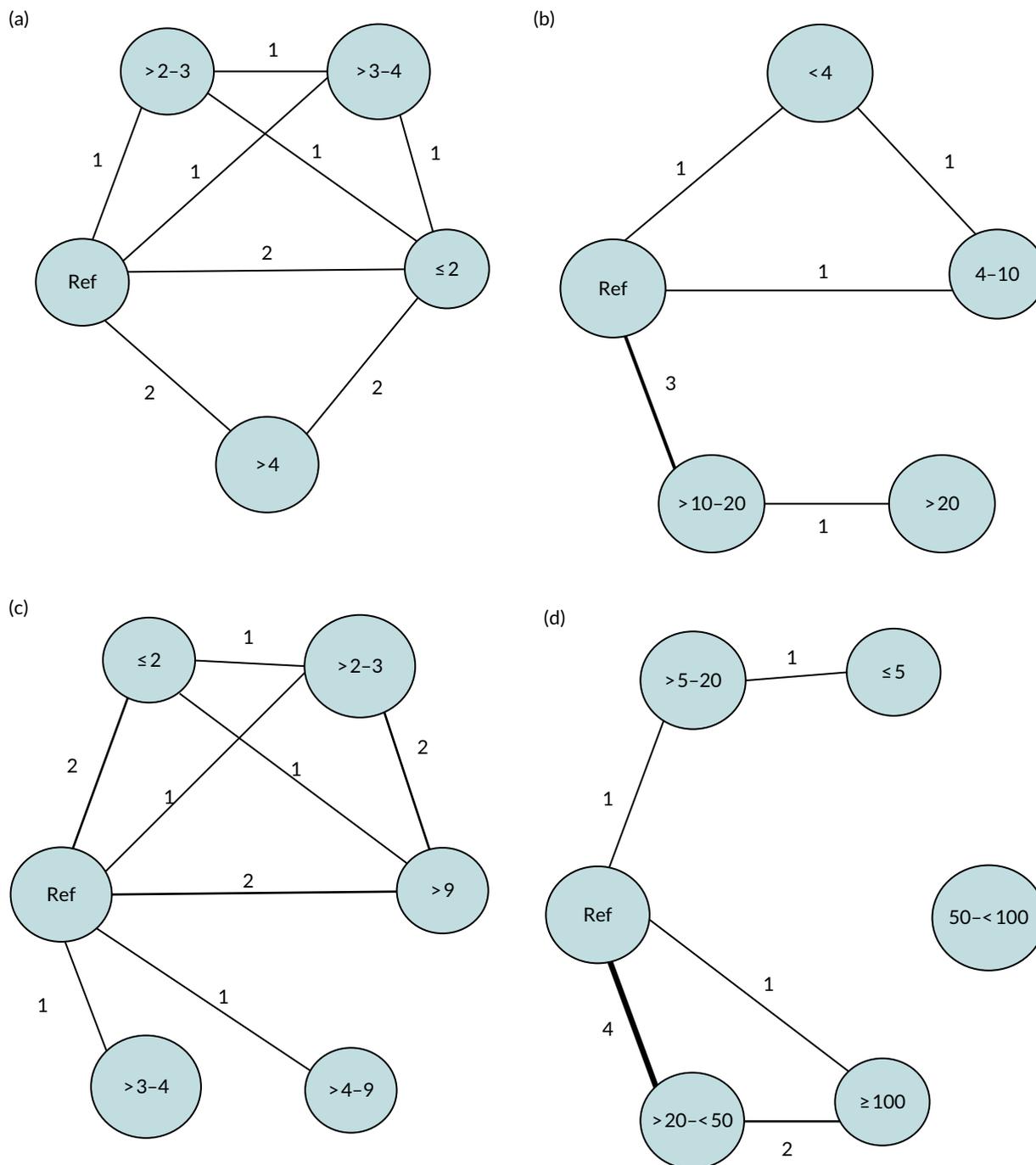


FIGURE 30 Network meta-analysis direct and indirect comparisons: auditory comprehension network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT approach by role; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) tailored SLT; (l) SLT tailored by difficulty; (m) SLT tailored by functional relevance; and (n) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference.



## Appendix 13 Network meta-analysis geometry for naming



**FIGURE 31** Network meta-analysis direct and indirect comparisons: naming network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT therapy approach by role; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) multimodal SLT; (l) tailored SLT; (m) SLT tailored by difficulty; (n) SLT tailored by functional relevance; and (o) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference. (*continued*)

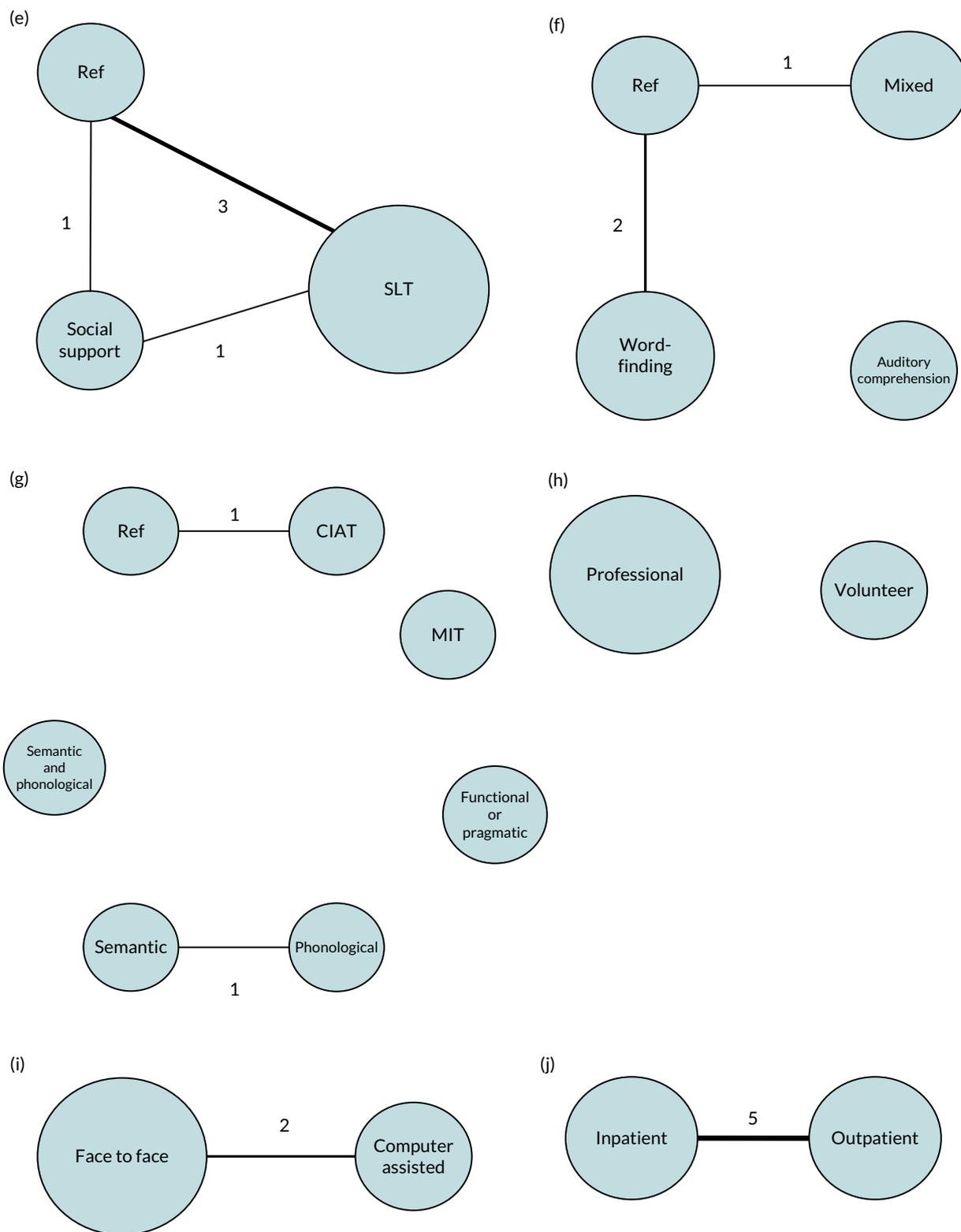
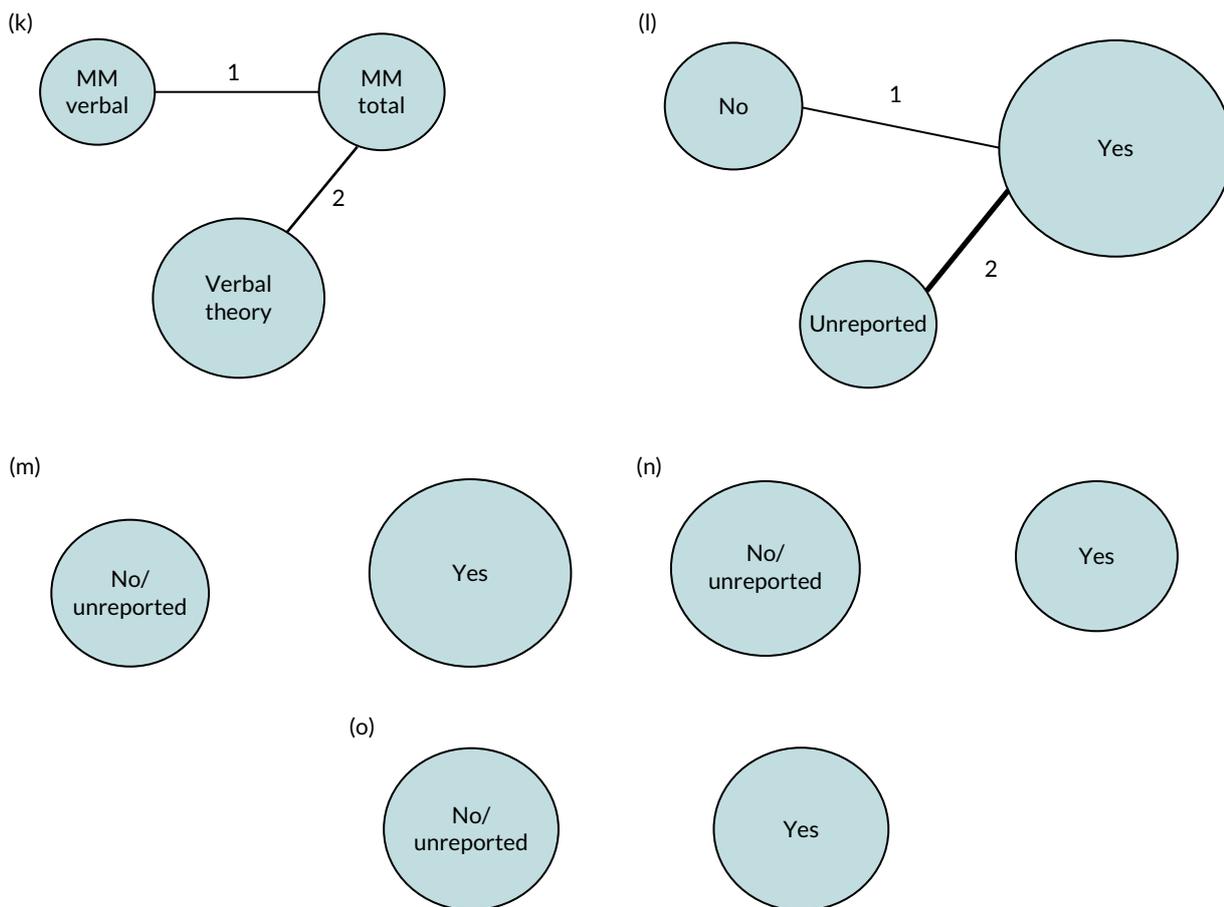


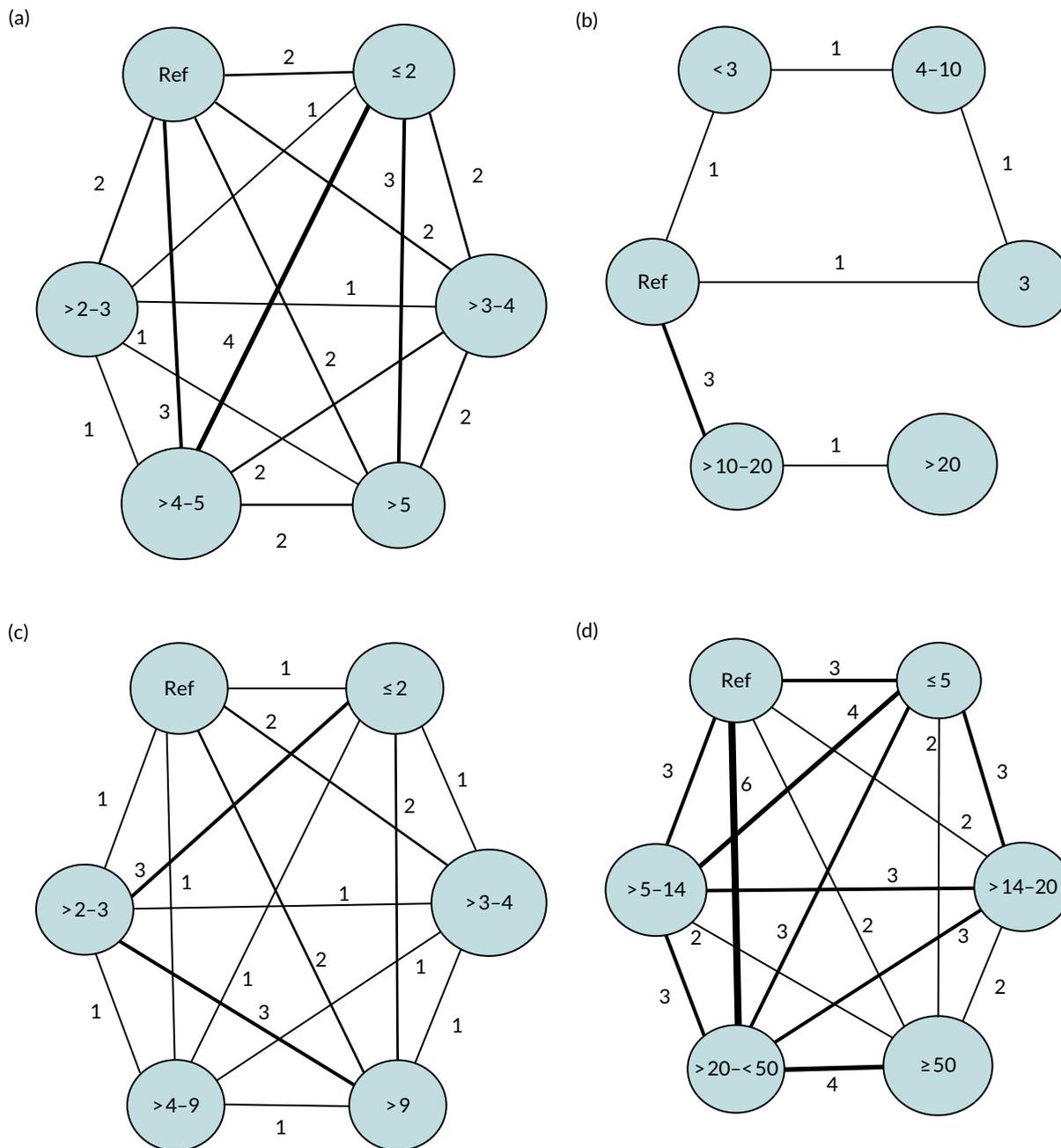
FIGURE 31 Network meta-analysis direct and indirect comparisons: naming network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT therapy approach by role; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) multimodal SLT; (l) tailored SLT; (m) SLT tailored by difficulty; (n) SLT tailored by functional relevance; and (o) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference. (continued)



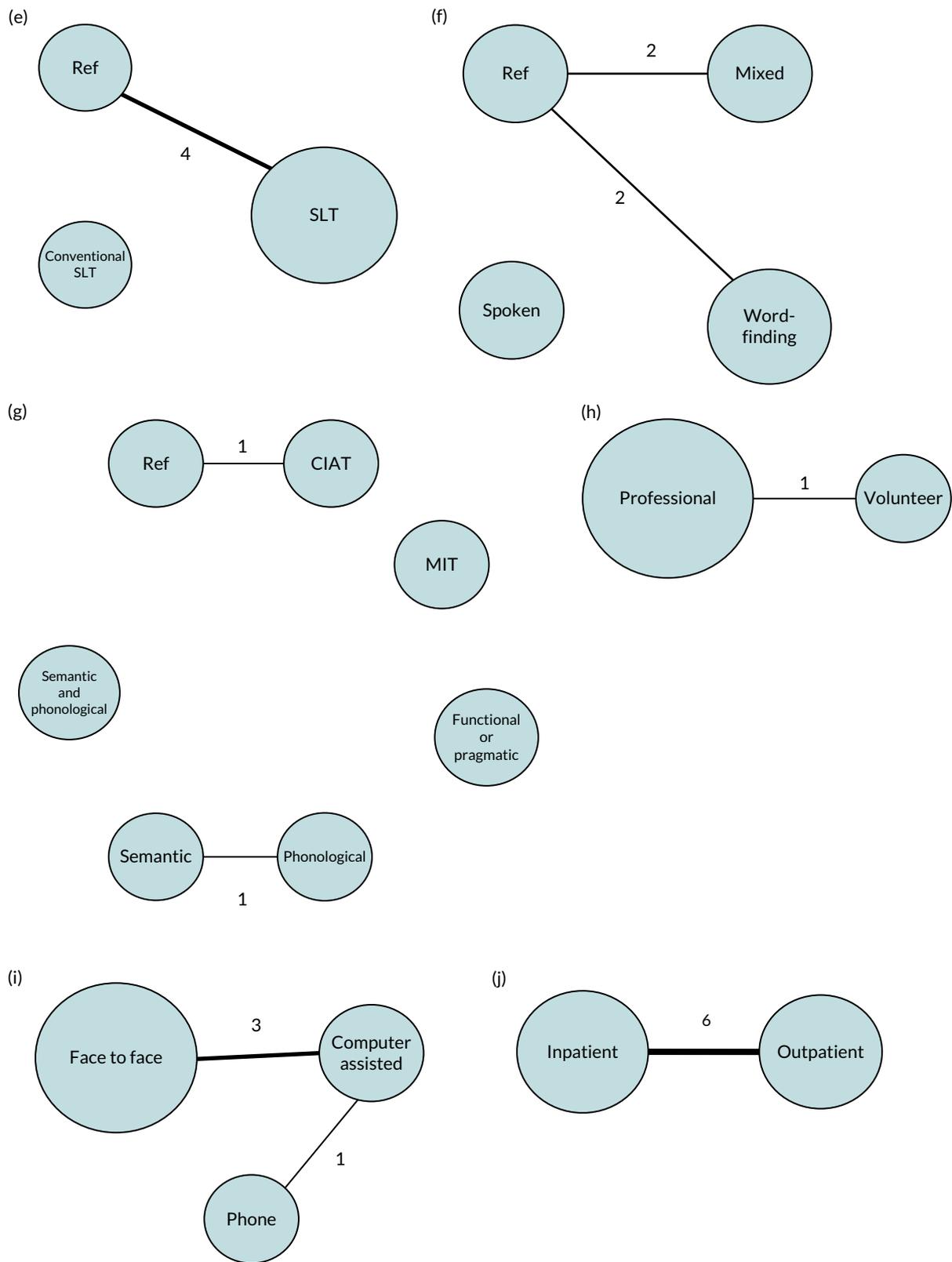
**FIGURE 31** Network meta-analysis direct and indirect comparisons: naming network geometry. (a) SLT frequency (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT therapy approach by role; (f) SLT approach by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) multimodal SLT; (l) tailored SLT; (m) SLT tailored by difficulty; (n) SLT tailored by functional relevance; and (o) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference.



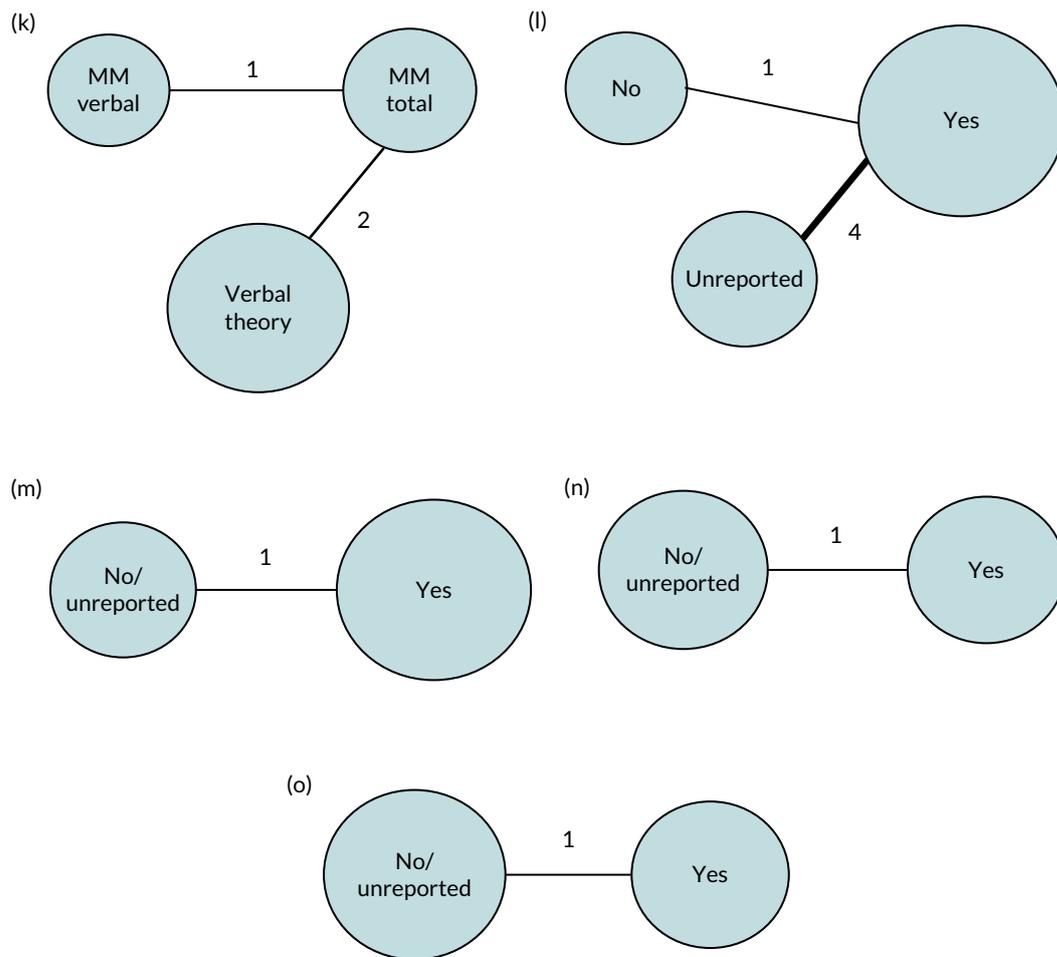
## Appendix 14 Network meta-analysis geometry for functional communication



**FIGURE 32** Network meta-analysis direct and indirect comparisons: functional communication (observer-rated) network geometry. (a) SLT (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT approach by role; (f) SLT by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) multimodal SLT; (l) tailored SLT; (m) SLT tailored by difficulty; (n) SLT tailored by functional relevance; and (o) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference. (*continued*)



**FIGURE 32** Network meta-analysis direct and indirect comparisons: functional communication (observer-rated) network geometry. (a) SLT (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT approach by role; (f) SLT by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) multimodal SLT; (l) tailored SLT; (m) SLT tailored by difficulty; (n) SLT tailored by functional relevance; and (o) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference. *(continued)*



**FIGURE 32** Network meta-analysis direct and indirect comparisons: functional communication (observer-rated) network geometry. (a) SLT (days per week); (b) SLT duration (weeks); (c) SLT intensity (hours per week); (d) SLT dosage (total hours); (e) SLT approach by role; (f) SLT by treatment target; (g) SLT by theoretical approach; (h) expertise of provider; (i) mode of SLT delivery; (j) context of SLT delivery; (k) multimodal SLT; (l) tailored SLT; (m) SLT tailored by difficulty; (n) SLT tailored by functional relevance; and (o) SLT home practice. CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy; MM, multimodal; Ref, reference.



## Appendix 15 Cluster-effect analysis

TABLE 19 Cluster-effect analysis; *p*-values for within-study clustering effect

Language domain outcome	Frequency	Duration	Intensity	Dosage
Overall severity	0.31	0 <sup>a</sup>	0 <sup>a</sup>	0 <sup>a</sup>
Auditory comprehension	0.076	0.10	0.097	0 <sup>a</sup>
Naming	0.11	0 <sup>a</sup>	0.20	0.30
Functional communication	0.24	0 <sup>a</sup>	0 <sup>a</sup>	0.15

a The G matrix was not positive definite.



## Appendix 16 Gains in language domains for regimen, approach and context

TABLE 20 Overview of highest significant gains in language domain outcomes by therapy regimen, approach and context

SLT component	Language domain			
	Overall language ability	Auditory comprehension	Naming	Functional communication
<b>Regimen</b>				
Frequency (number of SLT days weekly)	> 4	3 to 4	Up to 2	> 4
Duration (of SLT, in weeks)	≥ 10	3 or ≥ 10	≥ 20	≥ 4
Intensity (mean number of hours per week)	Up to 2; 3-4; ≥ 9	≥ 9	Up to 2	Up to 3
Dosage (total number of hours of SLT delivered)	20-50	20-50	Up to 5	14-20
Home practice tasks prescribed	Yes	Yes	No	No
<b>SLT approach</b>				
SLT target	Mixed	Word-finding	Word-finding	Mixed
Theoretical approach	Semantic/ phonological	Semantic/ phonological	Non-significant change from baseline	Functional/ pragmatic
Multimodal (verbal; total) or verbal approach	N/A	Non-significant change from baseline	No	Yes
Tailoring by functional relevance	Yes	Yes	Yes	Yes
Tailoring by difficulty	Yes	Yes	No	No
N/A, IPD was not available.				
<b>Note</b> Red denotes > 50% variance; green text denotes an unstable network.				



## Appendix 17 Frequency of speech and language therapy intervention by language outcome

TABLE 21 Frequency of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Frequency of SLT	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Up to 2 days weekly	5	90	10.24 (3.51 to 16.97)	6	92	9.73 (3.53 to 15.94)
> 2–3 days weekly	2	21	13.35 (4.29 to 22.41)	3	25	11.63 (3.49 to 19.77)
> 3–4 days weekly	5	76	13.08 (5.40 to 20.76)	9	171	13.92 (8.24 to 19.60)
> 4–5 days weekly	6	194	14.95 (8.67 to 21.23)	6	194	14.31 (8.37 to 20.25)
> 5 days weekly	2	32	14.14 (5.99 to 22.29)	4	75	13.15 (6.63 to 19.68)
Reference group	3	71	13.16 (5.74 to 20.58)	3	71	12.84 (5.76 to 19.92)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Up to 2 days weekly	4	64	-0.51 (-4.09 to 3.08)	5	68	1.62 (-1.80 to 5.03)
> 2–3 days weekly	4	89	1.86 (-2.06 to 5.78)	5	94	2.60 (-1.17 to 6.38)
> 3–4 days weekly	5	114	5.86 (1.64 to 10.01)	6	121	6.51 (2.58 to 10.45)
> 4–5 days weekly	8	171	4.63 (1.48 to 7.77)	11	206	6.19 (3.16 to 9.22)
> 5 days weekly	3	51	2.38 (-1.64 to 6.39)	7	101	3.64 (0.28 to 7.00)
Reference group	6	51	2.62 (-1.09 to 6.33)	6	51	3.92 (0.17 to 7.66)
<b>Naming (BNT, range 0–60)</b>						
Up to 2 days weekly	3	42	12.01 (6.52 to 17.59)	6	56	12.24 (7.35 to 17.12)
> 2–3 days weekly	3	84	6.45 (0.23 to 12.68)	4	89	7.19 (1.37 to 13.01)
> 3–4 days weekly	4	103	7.80 (1.23 to 14.37)	9	204	8.77 (4.28 to 13.26)
> 4 days weekly	6	104	4.07 (-0.93 to 9.08)	9	151	4.58 (0.34 to 8.82)
Reference group	5	52	7.25 (2.24 to 12.25)	5	52	7.81 (2.89 to 12.72)
<b>Reading comprehension (CAT reading subtest, range 0–74)</b>						
Up to 2 days weekly			-	0	0	-
> 2–3 days weekly			-	1	10	2.74 (-3.61 to 5.98)
> 3–4 days weekly			-	2	58	2.76 (-0.96 to 2.79)
≥ 5 days weekly			-	2	19	2.81 (-2.07 to 6.20)
Reference group			-	0	0	-

continued

TABLE 21 Frequency of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets (*continued*)

Frequency of SLT	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Functional communication (observer rated, AAT-SSC, range 0-5), inclusive of activity data</b>						
Up to 2 days weekly	5	82	0.52 (0.18 to 0.87)	5	82	0.49 (0.08 to 0.89)
> 2-3 days weekly	3	92	0.62 (0.22 to 1.01)	3	92	0.59 (0.12 to 1.06)
> 3-4 days weekly	4	102	0.70 (0.25 to 1.15)	6	126	0.88 (0.47 to 1.29)
> 4-5 days weekly	8	155	0.78 (0.48 to 1.09)	11	171	0.70 (0.33 to 1.07)
≥ 5 days weekly	3	9	0.66 (-0.01 to 1.33)	5	37	0.55 (0.06 to 1.03)
Reference group	6	85	0.45 (0.13 to 0.78)	6	85	0.42 (0.02 to 0.81)

a There were insufficient data for the analysis of frequency of SLT in relation to other spoken language or written language outcome measures.

Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.

## Appendix 18 Duration of speech and language therapy intervention by language outcome

TABLE 22 Duration of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Duration of SLT	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Up to 3 weeks	2	50	4.86 (–4.87 to 14.59)	3	74	7.12 (0.03 to 14.21)
3 weeks	3	158	13.13 (7.29 to 18.98)	3	158	12.29 (6.75 to 17.84)
4–10 weeks	4	78	12.16 (5.96 to 18.36)	7	110	10.94 (5.82 to 16.06)
> 10–20 weeks	3	45	17.27 (9.71 to 24.82)	6	126	16.76 (11.08 to 22.45)
> 20 weeks	2	34	16.93 (8.57 to 25.29)	3	43	17.57 (10.75 to 24.39)
Reference group	2	65	13.20 (6.39 to 20.02)	2	65	12.66 (6.12 to 19.21)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Up to 3 weeks	6	93	6.06 (0.84 to 11.29)	8	127	7.39 (2.80 to 11.98)
3 weeks	2	105	3.60 (–3.42 to 10.62)	2	105	4.63 (–0.75 to 10.01)
4–10 weeks	3	68	2.12 (–4.70 to 8.95)	6	113	2.98 (–1.97 to 7.93)
> 10–20 weeks	5	93	6.79 (1.69 to 11.88)	5	93	9.61 (4.51 to 14.71)
> 20 weeks	3	136	6.43 (1.55 to 11.30)	4	158	–0.91 (–6.69 to 4.87)
Reference group	5	45	5.49 (0.31 to 10.67)	5	45	7.74 (2.56 to 12.92)
<b>Naming (BNT, range 0–60)</b>						
Up to 4 weeks	5	86	5.68 (–0.42 to 11.79)	7	114	5.53 (0.37 to 10.69)
4–10 weeks	3	27	6.18 (–1.21 to 13.56)	6	89	8.02 (2.71 to 13.32)
> 10–20 weeks	4	86	7.30 (1.62 to 12.98)	6	106	8.49 (3.37 to 13.61)
> 20 weeks	3	134	8.38 (1.24 to 15.51)	4	191	8.73 (2.35 to 15.11)
Reference group	5	52	6.84 (1.22 to 12.47)	5	52	7.86 (2.53 to 13.18)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>						
Up to 3 weeks	4	55	0.40 (–0.07 to 0.87)	4	55	0.33 (–0.24 to 0.90)
3 weeks	2	56	0.66 (0.22 to 1.10)	2	71	0.52 (0.10 to 0.93)
4–10 weeks	2	57	0.80 (0.29 to 1.31)	2	110	0.79 (0.39 to 1.19)
> 10–20 weeks	4	76	0.77 (0.40 to 1.15)	4	76	0.67 (0.20 to 1.14)
> 20 weeks	4	151	0.76 (0.34 to 1.18)	4	151	0.65 (0.10 to 1.20)
Reference group	5	79	0.44 (0.08 to 0.80)	5	79	0.33 (–0.10 to 0.76)

<sup>a</sup> There were insufficient data for the analysis of frequency of SLT in relation to other spoken language or written language outcome measures.

Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 19 Intensity of speech and language therapy intervention by language outcome

TABLE 23 Intensity of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Intensity of SLT (hours per week)	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Up to 2 hours	3	74	15.85 (8.06 to 23.64)	4	86	13.65 (6.94 to 20.36)
> 2–3 hours	7	93	10.18 (4.03 to 16.32)	7	93	9.56 (3.31 to 15.82)
> 3–4 hours	4	104	15.80 (8.85 to 22.74)	5	118	15.88 (9.49 to 22.28)
> 4–9 hours	2	50	12.22 (4.53 to 19.91)	5	151	12.84 (6.95 to 18.74)
> 9 hours	3	96	15.64 (9.14 to 22.13)	4	115	14.98 (9.34 to 20.62)
Reference group	2	65	14.37 (6.68 to 22.07)	2	65	14.40 (7.08 to 21.73)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Up to 2 hours	2	19	6.50 (1.72 to 11.27)	4	39	6.80 (2.83 to 10.78)
> 2–3 hours	7	120	0.32 (–3.11 to 3.75)	8	122	0.70 (–2.87 to 4.27)
> 3–4 hours	3	112	6.01 (1.04 to 10.98)	5	115	4.15 (–0.45 to 8.76)
> 4–9 hours	5	103	2.47 (–0.97 to 5.92)	7	126	2.99 (–0.38 to 6.36)
> 9 hours	6	141	7.30 (4.09 to 10.52)	10	194	7.63 (4.58 to 10.67)
Reference group	5	45	2.43 (–1.44 to 6.29)	5	45	2.75 (–1.21 to 6.71)
<b>Naming (BNT, range 0–60)</b>						
Up to 2 hours	2	18	13.23 (5.83 to 20.64)	3	34	12.87 (6.25 to 19.50)
> 2–3 hours	5	101	6.05 (–0.06 to 12.17)	6	111	7.31 (1.56 to 13.05)
> 3–4 hours	3	127	9.70 (2.70 to 16.69)	3	127	10.90 (3.66 to 18.15)
> 4–9 hours	2	41	5.71 (–2.08 to 13.50)	5	124	8.06 (2.57 to 13.55)
> 9 hours	4	46	2.87 (–3.24 to 8.98)	8	104	3.65 (–1.36 to 8.67)
Reference group	5	52	7.47 (1.78 to 13.17)	5	52	8.54 (3.14 to 13.95)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>						
Up to 2 hours	4	83	0.77 (0.36 to 1.19)	6	134	0.75 (0.36 to 1.13)
> 2–3 hours	5	73	0.76 (0.34 to 1.18)	6	75	0.70 (0.27 to 1.12)
> 3–4 hours	5	178	0.70 (0.35 to 1.06)	6	180	0.69 (0.29 to 1.08)
> 4–9 hours	3	59	0.53 (0.13 to 0.92)	4	73	0.68 (0.30 to 1.05)
> 9 hours	6	60	0.69 (0.33 to 1.06)	10	106	0.51 (0.17 to 0.85)
Reference group	5	79	0.41 (0.06 to 0.76)	5	79	0.40 (0.02 to 0.79)

<sup>a</sup> There were insufficient data for the analysis of frequency of SLT in relation to other spoken language or written language outcome measures.

Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 20 Dosage of speech and language therapy intervention by language outcome

TABLE 24 Dosage of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Dosage (total number of hours of SLT)	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Up to 5 hours	6	101	9.71 (3.94 to 15.48)	7	106	8.79 (3.29 to 14.29)
> 5–14 hours	4	114	15.08 (9.31 to 20.85)	6	145	13.67 (8.58 to 18.76)
> 14–20 hours	4	89	14.63 (8.73 to 20.53)	4	89	13.64 (7.79 to 19.49)
> 20–< 50 hours	4	31	18.37 (10.58 to 26.16)	5	33	17.98 (10.83 to 25.12)
≥ 50 hours	4	68	13.87 (7.04 to 20.71)	8	176	14.74 (9.86 to 19.63)
Reference group	4	77	11.63 (5.22 to 18.04)	4	77	10.74 (4.71 to 16.77)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Up to 5 hours	3	64	0.23 (–4.09 to 4.54)	5	71	1.99 (–1.79 to 5.77)
> 5–14 hours	4	86	1.42 (–2.67 to 5.51)	7	90	2.83 (–0.60 to 6.26)
> 14–20 hours	2	66	3.72 (–0.62 to 8.07)	3	66	5.11 (1.16 to 9.07)
> 20–< 50 hours	7	90	5.23 (1.51 to 8.95)	9	105	6.01 (2.45 to 9.58)
≥ 50 hours	6	183	4.18 (0.30 to 8.06)	9	227	5.89 (2.50 to 9.27)
Reference group	6	51	3.46 (–0.42 to 7.34)	6	51	4.43 (0.55 to 8.32)
<b>Naming (BNT, range 0–60)</b>						
Up to 5 hours	2	28	12.48 (1.34 to 23.63)	3	35	8.05 (–0.17 to 16.28)
> 5–20 hours	4	61	5.35 (–2.85 to 13.55)	5	70	5.44 (–1.35 to 12.24)
> 20–< 50 hours	5	81	9.23 (1.75 to 16.70)	8	135	11.32 (5.92 to 16.72)
> 50–99 hours	2	122	7.56 (–6.73 to 21.85)	5	162	7.24 (–1.07 to 15.56)
≥ 100 hours	3	41	–0.85 (–9.46 to 7.77)	5	98	2.22 (–4.39 to 8.83)
Reference group	5	52	7.85 (0.42 to 15.28)	5	52	9.66 (3.87 to 15.45)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>						
Up to 5 hours	3	47	0.29 (–0.13 to 0.72)	4	48	0.33 (–0.14 to 0.80)
> 5–14 hours	5	104	0.68 (0.33 to 1.03)	6	107	0.70 (0.29 to 1.11)
> 14–20 hours	3	11	0.94 (0.34 to 1.55)	4	12	0.91 (0.31 to 1.52)
> 20–< 50 hours	9	96	0.77 (0.43 to 1.10)	11	127	0.81 (0.43 to 1.20)
≥ 50 hours	7	174	0.73 (0.37 to 1.08)	10	205	0.62 (0.25 to 0.98)
Reference group	7	91	0.40 (0.07 to 0.73)	7	91	0.42 (0.03 to 0.82)

<sup>a</sup> There were insufficient data for the analysis of frequency of SLT in relation to other spoken language or written language outcome measures.

Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 21 Home practice speech and language therapy tasks by language outcome

TABLE 25 Home practice SLT tasks by language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Home practice	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Yes	2	87	16.69 (10.01 to 23.37)	3	101	16.56 (10.69 to 22.43)
No	10	330	13.35 (8.21 to 18.48)	15	462	13.05 (8.80 to 17.30)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Yes	7	278	5.28 (2.19 to 8.37)	8	300	6.68 (3.60 to 9.77)
No	10	217	2.27 (–0.67 to 5.22)	15	296	3.53 (0.83 to 6.23)
<b>Naming (BNT, range 0–60)</b>						
Yes	4	167	6.94 (–0.57 to 14.46)	5	224	7.34 (0.26 to 14.42)
No	9	166	7.08 (1.81 to 12.35)	15	265	8.06 (3.70 to 12.43)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>						
Yes	5	187	0.61 (0.18 to 1.04)	5	187	0.69 (0.34 to 1.04)
No	10	267	0.74 (0.39 to 1.09)	14	371	0.55 (0.03 to 1.07)

a There were insufficient data for the analysis of other spoken language or written language outcome measures. Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 22 Target of speech and language therapy intervention by language outcome

TABLE 26 Target of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Target	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Mixed	8	245	15.62 (8.82 to 22.43)	9	259	17.77 (9.48 to 26.07)
Spoken language	2	70	12.83 (–0.99 to 26.64)	3	94	15.31 (5.33 to 25.30)
Auditory comprehension	1	6	11.91 (–7.05 to 30.87)	1	6	21.12 (0.34 to 41.90)
Word-finding	0	0	–	2	21	11.08 (–4.33 to 26.48)
Reference group	2	65	12.23 (3.75 to 20.70)	2	65	16.65 (7.13 to 26.17)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Mixed	5	142	3.37 (–1.20 to 7.93)	6	164	5.38 (0.49 to 10.27)
Spoken language	0	0	–	1	22	3.69 (–7.41 to 14.78)
Auditory comprehension	2	17	1.25 (–7.58 to 10.09)	2	17	2.48 (–6.84 to 11.79)
Word-finding	7	136	4.46 (0.31 to 8.62)	9	196	5.61 (1.10 to 10.12)
Reading	0	0	–	1	10	1.53 (–10.18 to 13.24)
Reference group	4	29	2.54 (–2.40 to 7.47)	4	29	3.98 (–1.61 to 9.57)
<b>Naming (BNT, range 0–60)</b>						
Mixed	4	84	7.33 (0.58 to 14.08)	4	84	8.97 (2.08 to 15.86)
Auditory comprehension	2	25	0.33 (–11.29 to 11.95)	3	41	1.59 (–7.40 to 10.58)
Word-finding	7	174	8.82 (3.15 to 14.49)	13	268	10.00 (5.44 to 14.56)
Reference group	3	27	10.24 (3.56 to 16.92)	3	27	11.66 (5.19 to 18.13)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>						
Mixed	3	72	1.05 (0.52 to 1.58)	3	72	1.02 (0.41 to 1.63)
Spoken language	1	52	0.68 (–0.40 to 1.77)	1	52	0.67 (–0.49 to 1.83)
Word-finding	8	184	0.72 (0.33 to 1.10)	11	242	0.67 (0.21 to 1.12)
Reading	0	0	–	1	10	1.00 (–0.28 to 2.28)
Reference group	4	58	0.75 (0.26 to 1.23)	4	58	0.72 (0.14 to 1.29)

a There were insufficient data for the analysis of other spoken language or written language outcome measures. Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 23 Theoretical approach to speech and language therapy intervention by language outcome

TABLE 27 Theoretical approach to SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Theoretical approach	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Semantic/phonological	2	60	20.39 (1.90 to 38.88)	3	74	16.55 (4.93 to 28.16)
Phonological	0	0	–	2	21	9.07 (–7.34 to 25.49)
CIAT	1	10	16.11 (–4.87 to 37.09)	2	34	12.60 (–0.19 to 25.38)
Functional/pragmatic	2	83	13.50 (–1.48 to 28.47)	2	83	8.18 (–9.27 to 25.63)
Reference group	2	65	23.46 (4.98 to 41.95)	2	65	18.46 (3.00 to 33.92)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Semantic/phonological	1	35	11.93 (1.44 to 22.43)	2	45	8.05 (1.42 to 14.68)
Semantic	1	27	3.29 (–4.90 to 11.48)	1	27	2.62 (–3.96 to 9.21)
Phonological	2	45	5.95 (–1.56 to 13.46)	3	63	5.32 (–0.35 to 10.99)
CIAT	2	32	7.46 (0.67 to 14.25)	3	54	6.02 (0.25 to 11.79)
MIT	1	23	0.26 (–10.08 to 10.59)	1	23	1.42 (–11.14 to 8.31)
Functional/pragmatic	3	98	5.52 (–0.86 to 11.91)	3	98	3.89 (–2.86 to 10.63)
Reference group	4	29	2.33 (–3.53 to 8.20)	4	29	0.63 (–5.29 to 6.55)
<b>Naming (BNT, range 0–60)</b>						
Semantic/phonological	1	35	19.38 (–13.50 to 52.27)	2	45	15.48 (–0.53 to 31.49)
Semantic	1	26	–2.48 (–35.82 to 30.87)	1	26	2.75 (–11.13 to 16.62)
Phonological	1	25	–1.66 (–34.92 to 31.60)	2	54	4.08 (–9.30 to 17.45)
CIAT	1	13	15.53 (–4.48 to 35.55)	2	18	12.43 (–0.91 to 25.77)
MIT	1	20	–2.25 (–35.04 to 30.53)	1	20	1.00 (–22.78 to 24.78)
Functional/pragmatic	2	32	4.91 (–18.39 to 28.22)	3	64	10.61 (–3.01 to 24.23)
Reference group	3	27	14.78 (–4.60 to 34.15)	3	27	13.51 (0.30 to 26.71)
<b>Functional communication (observer rated, AAT-SSC range 0–5), inclusive of activity data</b>						
Semantic/phonological	3	100	0.71 (–0.15 to 1.55)	4	110	0.77 (0.18 to 1.37)
Semantic	1	26	0.35 (–1.15 to 1.86)	1	26	0.25 (–0.53 to 1.03)
Phonological	1	25	0.37 (–1.11 to 1.84)	2	44	0.28 (–0.42 to 0.97)
CIAT	1	13	0.77 (–0.22 to 1.75)	2	18	0.57 (–0.14 to 1.28)
MIT	1	24	0.20 (–1.11 to 1.50)	1	24	0.18 (–0.85 to 1.21)
Functional/pragmatic	1	8	1.82 (0.36 to 3.28)	2	36	1.60 (0.83 to 2.36)
Reference group	4	58	0.68 (–0.10 to 1.46)	4	58	0.61 (–0.04 to 1.26)

CIAT, constraint-induced aphasia therapy; MIT, melodic intonation therapy.

a Insufficient data on other spoken language, reading comprehension and writing.

Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 24 Multimodal and verbal speech and language therapy theoretical approach by language outcome

TABLE 28 Multimodal and verbal SLT theoretical approach and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

SLT approach	RCT data		Estimate of mean		All data		Estimate of mean	
	only (n)	IPD (n)	Yes/no	(95% CI)	sets (n)	IPD (n)	Yes/no	(95% CI)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>								
Multimodal verbal	2	45	Yes	2.23 (–13.21 to 17.67)	2	45	Yes	7.23 (–2.89 to 17.34)
			No	3.84 (–0.22 to 7.91)			No	4.88 (1.20 to 8.57)
Multimodal total	3	67	Yes	2.63 (–12.21 to 17.48)	4	89	Yes	7.49 (–1.82 to 16.80)
			No	3.44 (–0.97 to 7.85)			No	4.62 (0.52 to 8.71)
Verbal approach	13	299	Yes	1.59 (–13.20 to 16.38)	19	400	Yes	6.36 (–2.88 to 15.61)
			No	4.49 (–0.62 to 9.59)			No	5.75 (0.91 to 10.58)
<b>Naming (BNT, range 0–60)</b>								
Multimodal verbal	2	47	Yes	8.02 (–9.45 to 25.50)	3	57	Yes	8.00 (–10.18 to 26.16)
			No	6.83 (2.00 to 11.67)			No	6.97 (2.11 to 11.83)
Multimodal total	3	60	Yes	6.86 (–9.80 to 23.51)	3	60	Yes	6.75 (–10.78 to 24.29)
			No	8.00 (2.80 to 13.21)			No	8.21 (3.26 to 13.16)
Verbal approach	11	224	Yes	7.32 (–9.27 to 23.92)	16	308	Yes	7.21 (–10.27 to 24.69)
			No	7.53 (1.51 to 13.56)			No	7.75 (2.01 to 13.50)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>								
Multimodal verbal	2	38	Yes	1.96 (0.85 to 3.07)	2	38	Yes	1.95 (0.68 to 3.22)
			No	0.57 (0.28 to 0.86)			No	0.65 (0.29 to 1.00)
Multimodal total	3	66	Yes	1.90 (0.86 to 2.93)	3	66	Yes	1.89 (0.68 to 3.09)
			No	0.63 (0.32 to 0.95)			No	0.71 (0.32 to 1.10)
Verbal approach	10	273	Yes	1.95 (0.92 to 2.99)	10	335	Yes	1.94 (0.75 to 3.14)
			No	0.58 (0.19 to 0.97)			No	0.65 (0.19 to 1.11)

<sup>a</sup> There were insufficient data for the analysis of other spoken language or written language outcome measures. Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 25 Expertise and delivery of speech and language therapy intervention by language outcome

TABLE 29 Expertise and delivery of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

SLT provider	RCT data only (n)		IPD (n)	Yes/no	Estimate of mean (95% CI)	All data sets (n)		IPD (n)	Yes/no	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>										
Professional	11	405	Yes		14.75 (6.97 to 22.53)	16	532	Yes		13.34 (5.79 to 20.89)
				No	11.52 (3.93 to 19.11)				No	12.43 (5.22 to 19.64)
Non-professional	1	12	Yes		14.18 (1.79 to 26.57)	1	12	Yes		12.83 (0.59 to 25.07)
				No	12.09 (6.43 to 17.74)				No	12.94 (8.34 to 17.54)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>										
Professional	16	485	Yes		5.16 (0.55 to 9.78)	19	546	Yes		6.57 (2.90 to 10.25)
				No	4.08 (–0.36 to 8.51)				No	5.56 (1.83 to 9.29)
Non-professional	1	10	Yes		6.28 (–1.25 to 13.81)	2	3	Yes		8.11 (2.35 to 13.87)
				No	2.96 (0.02 to 5.91)				No	4.03 (1.28 to 6.77)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>										
Professional	14	447	Yes		0.52 (0.06 to 0.99)	17	533	Yes		0.49 (0.01 to 0.96)
				No	0.31 (–0.24 to 0.86)				No	0.26 (–0.28 to 0.81)
Non-professional	1	9	Yes		0.61 (0.32 to 0.90)	1	9	Yes		0.18 (–0.67 to 1.03)
				No	0.22 (–0.64 to 1.08)				No	0.57 (0.28 to 0.86)

a Insufficient data on participants' naming, other spoken language, reading comprehension or writing following non-professional delivery of SLT intervention.

\*There was insufficient data for the analysis of other spoken language or written language outcome measures. Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 26 Context of delivery of speech and language therapy by language outcome

TABLE 30 Context of delivery of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

SLT context	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Inpatient	10	306	13.64 (8.76 to 18.52)	14	431	13.38 (9.10 to 17.66)
Not an inpatient			13.46 (7.98 to 18.94)			14.16 (9.31 to 19.01)
Outpatient	6	207	15.00 (9.77 to 20.22)	7	226	14.48 (9.71 to 19.26)
Not an outpatient			12.11 (7.00 to 17.22)			13.06 (8.73 to 17.39)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Inpatient	12	348	3.62 (0.81 to 6.43)	15	409	4.77 (2.08 to 7.45)
Not an inpatient			3.17 (–0.01 to 6.35)			4.10 (1.00 to 7.19)
Outpatient	9	289	3.82 (0.91 to 6.72)	13	351	5.09 (2.37 to 7.93)
Not an outpatient			2.98 (–0.14 to 6.09)			3.77 (0.70 to 6.85)
<b>Naming (BNT, range 0–60)</b>						
Inpatient	11	298	6.89 (2.47 to 11.30)	14	403	7.37 (3.39 to 11.36)
Not an inpatient			6.77 (1.16 to 12.38)			6.96 (2.40 to 11.50)
Outpatient	6	204	7.18 (1.62 to 12.73)	9	267	7.63 (3.00 to 12.26)
Not an outpatient			6.48 (1.76 to 11.21)			6.70 (2.60 to 10.81)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>						
Inpatient	11	376	0.70 (0.44 to 0.96)	13	451	0.67 (0.40 to 0.95)
Not an inpatient			0.59 (0.30 to 0.88)			0.54 (0.26 to 0.83)
Outpatient	9	271	0.74 (0.46 to 1.01)	12	328	0.52 (0.24 to 0.80)
Not an outpatient			0.56 (0.29 to 0.83)			0.70 (0.42 to 0.98)

<sup>a</sup> There were insufficient data for the analysis of other spoken language or written language outcome measures. Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 27 Mode of delivery of speech and language therapy intervention by language outcome

TABLE 31 Mode of delivery of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Delivery mode	RCT data only (n)	IPD (n)	Yes/no	Estimate of mean (95% CI)	IPD (n)	Yes/no	Estimate of mean (95% CI)	
<b>Overall language ability (WAB-AQ, range 0–100)</b>								
Face to face	11	351	Yes	14.13 (8.34 to 19.91)	16	478	Yes	14.90 (9.34 to 20.47)
			No	11.06 (2.63 to 19.49)			No	14.18 (5.61 to 22.74)
Computer assisted	1	62	Yes	12.26 (6.92 to 17.61)	2	81	Yes	13.50 (4.74 to 22.26)
			No	12.92 (3.45 to 22.39)			No	15.58 (2.70 to 28.46)
Self-managed	-	-	-	-	1	62	Yes	16.98 (2.09 to 31.87)
			No	-			No	12.10 (4.00 to 20.20)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>								
Face to face	14	390	Yes	5.06 (1.76 to 8.37)	18	461	Yes	6.46 (3.16 to 9.76)
			No	5.04 (0.08 to 10.00)			No	6.50 (1.72 to 11.28)
Computer assisted	4	145	Yes	5.10 (0.85 to 9.34)	6	173	Yes	6.30 (2.47 to 10.15)
			No	5.01 (-0.67 to 10.68)			No	6.66 (1.45 to 11.86)
Self-managed	1	66	Yes	6.74 (-0.09 to 13.58)	1	66	Yes	8.44 (2.08 to 14.80)
			No	3.36 (-0.11 to 6.83)			No	4.52 (1.45 to 7.58)
<b>Naming (BNT, range 0–60)</b>								
Face to face	12	325	Yes	5.71 (0.11 to 11.30)	17	429	Yes	7.06 (2.66 to 11.47)
			No	5.94 (-0.53 to 12.41)			No	7.44 (2.40 to 12.47)
Computer assisted	2	58	Yes	4.38 (-5.15 to 13.90)	4	87	Yes	6.51 (-0.63 to 13.66)
			No	7.27 (2.62 to 11.92)			No	7.99 (4.04 to 11.93)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>								
Face to face	12	366	Yes	0.70 (0.20 to 1.19)	15	434	Yes	0.67 (0.16 to 1.18)
			No	0.46 (-0.05 to 0.96)			No	0.45 (-0.07 to 0.96)
Computer assisted	4	76	Yes	0.72 (0.06 to 1.37)	6	105	Yes	0.41 (-0.10 to 0.91)
			No	0.43 (-0.09 to 0.96)			No	0.71 (0.07 to 1.34)

<sup>a</sup> There were insufficient data for the analysis of other spoken language or written language outcome measures. Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 28 Functional relevance of speech and language therapy intervention by language outcome

TABLE 32 Tailoring the functional relevance of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Functional relevance	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Tailored	6	232	16.47 (10.95 to 21.99)	6	232	16.76 (11.28 to 22.23)
Not tailored	7	185	12.05 (6.90 to 17.20)	13	331	12.72 (8.44 to 17.00)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Tailored	7	194	5.26 (2.05 to 8.47)	7	194	6.71 (3.35 to 10.08)
Not tailored	10	301	2.43 (–0.57 to 5.43)	16	402	3.91 (1.14 to 6.68)
<b>Naming (BNT, range 0–60)</b>						
Tailored	5	113	8.79 (1.95 to 15.63)	14	145	12.38 (6.02 to 18.74)
Not tailored	8	220	5.95 (0.57 to 11.32)	6	298	6.68 (2.43 to 10.93)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>						
Tailored	6	249	0.74 (0.38 to 1.10)	10	336	0.75 (0.36 to 1.13)
Not tailored	8	195	0.71 (0.32 to 1.11)	9	223	0.57 (0.24 to 0.90)

<sup>a</sup> There were insufficient data for the analysis of other spoken language or written language outcome measures. Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 29 Level of difficulty of speech and language therapy intervention by language outcome

TABLE 33 Tailoring level of difficulty of SLT intervention and language outcome by domain;<sup>a</sup> multivariable estimates of means (95% CIs) for RCTs and all data sets

Level of difficulty	RCT data only (n)	IPD (n)	Estimate of mean (95% CI)	All data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Overall language ability (WAB-AQ, range 0–100)</b>						
Tailored for difficulty	7	210	14.46 (8.82 to 20.09)	10	267	14.11 (9.31 to 18.91)
Not tailored	6	207	13.24 (7.50 to 18.99)	9	296	13.00 (8.18 to 17.82)
<b>Auditory comprehension (TT-AAT, range 0–50)</b>						
Tailored for difficulty	10	331	4.57 (1.55 to 7.60)	12	371	5.73 (2.69 to 8.78)
Not tailored	7	164	1.95 (–1.30 to 5.20)	11	225	3.34 (0.36 to 6.31)
<b>Naming (BNT, range 0–60)</b>						
Tailored for difficulty	9	254	5.66 (0.74 to 10.58)	11	362	7.26 (2.48 to 12.03)
Not tailored	4	79	10.21 (2.75 to 17.67)	9	138	8.61 (3.40 to 13.82)
<b>Functional communication (observer rated, AAT-SSC, range 0–5), inclusive of activity data</b>						
Tailored for difficulty	10	313	0.65 (0.32 to 0.98)	12	360	0.59 (0.23 to 0.95)
Not tailored	5	141	0.81 (0.34 to 1.27)	8	208	0.70 (0.31 to 1.10)

a There were insufficient data for the analysis of other spoken language or written language outcome measures. Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.



## Appendix 30 Subgroup analysis summary of significant gains

TABLE 34 Subgroup analysis summary of greatest significant gains (95% CI) from baseline by SLT regimen and language domain, IPD (RCTs) and GRADE

SLT regimen	Overall language ability (WAB-AQ, score 0–100 points)	Auditory comprehension (TT-AAT, score 0–50 points)	Naming (BNT, score 0–60 points)	Functional communication (AAT-SSC, score 0–5 points)	GRADE rating
<i>Frequency of SLT (days per week)</i>					
<i>Age group</i>					
Younger ( $\leq 65$ years) (95% CI)	15.12 (8.2 to 22.1) SLT 5 days weekly	6.78 (2.3 to 11.2) SLT 4 days weekly	15.02 (8.9 to 21.1) SLT $\leq 2$ days weekly	1.18 (0.28 to 2.08) SLT $> 5$ days weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 107 (6)	IPD 64 (5)	IPD 26 (4)	IPD 3 (2)	
Older ( $> 65$ years) (95% CI)	17.19 (3.9 to 30.5) SLT $> 5$ days weekly	8.48 (2.0 to 14.9) SLT 4 days weekly	9.83 (2.4 to 17.2) SLT $\leq 2$ days weekly	0.78 (0.15 to 1.4) SLT $> 3$ to 4 days weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 10 (2)	IPD 50 (3)	IPD 16 (4)	IPD 54 (3)	
<i>Time after aphasia onset</i>					
SLT $\leq 3$ months from aphasia onset (95% CI)	21.4 (13.5 to 29.4) SLT 5 days weekly	NS	17.0 (7.7 to 26.2) SLT $\leq 2$ days weekly	1.6 (0.59 to 2.5) SLT 4 days weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 150 (5)		IPD 33 (3)	IPD 80 (1)	
SLT $> 3$ months from aphasia onset (95% CI)	6.3 (1.6 to 11.1) SLT 5 days weekly	3.7 (1.4 to 6.0) SLT 4 to 5 days weekly	2.8 (0.6 to 5.0) SLT 3 days weekly	NS	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 44 (1)	IPD 89 (5)	IPD 78 (3)		
<i>Aphasia severity</i>					
Mild–moderate aphasia (95% CI)	9.9 (4.4 to 15.3) SLT $> 5$ days weekly	NS	11.1 (5.6 to 16.6) SLT $\geq 3$ to 5 days weekly	0.7 (0.4 to 1.0) SLT $\geq 4$ days weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 16 (2)		IPD 11 (3)	IPD 55 (8)	
Moderate–severe aphasia (95% CI)	18.2 (8.0 to 28.5) SLT $\geq 3$ days weekly	8.5 (3.7 to 13.3) SLT 4 days weekly	13.1 (7.0 to 19.1) SLT $\leq 2$ days weekly	1.0 (0.5 to 1.5) SLT 4 days weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 38 (5)	IPD 80 (5)	IPD 36 (4)	IPD 55 (2)	

SLT regimen	Overall language ability (WAB-AQ, score 0–100 points)	Auditory comprehension (TT-AAT, score 0–50 points)	Naming (BNT, score 0–60 points)	Functional communication (AAT-SSC, score 0–5 points)	GRADE rating
<b>Sex</b>					
Female (95% CI)	24.2 (7.7 to 40.7) SLT 3 days weekly	8.1 (2.7 to 13.6) SLT 4 days weekly	17.1 (9.5 to 24.6) SLT ≤ 2 days weekly	1.0 (0.2 or 1.8) SLT 4 days weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 5 (2)	IPD 52 (5)	IPD 17 (4)	IPD 49 (3)	
Male (95% CI)	13.6 (4.3 or 22.9) SLT > 5 days weekly	5.1 (1.4 to 8.7) SLT > 4 to 5 days weekly	10.6 (4.3 to 16.7) SLT ≤ 2 days weekly	0.8 (0.09 to 1.5) SLT > 5 days weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 21 (2)	IPD 99 (8)	IPD 25 (4)	IPD 6 (3)	
<b>Duration of SLT (in weeks)</b>					
<b>Age group</b>					
Younger (≤ 65 years) (95% CI)	22.7 (15.2 to 30.2) > 10–20 weeks of SLT	8.4 (2.6 to 14.2) > 10–20 weeks of SLT	11.3 (5.4 to 17.1) > 10–20 weeks of SLT	1.2 (0.63 to 1.8) 3 to 10 weeks of SLT	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 25 (3)	IPD 60 (5)	IPD 59 (4)	IPD 27 (2)	
Older (> 65 years) (95% CI)	20.6 (7.8 to 33.4) > 20 weeks of SLT	NS	11.2 (2.0 to 20.4) > 20 weeks of SLT	1.3 (0.5 to 2.1) 4–10 weeks of SLT	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 15 (2)		IPD 71 (3)	IPD 9 (2)	
<b>Time after aphasia</b>					
SLT ≤ 3 months from aphasia onset (95% CI)	24.7 (12.5 to 36.9) > 4 weeks of SLT	8.8 (1.2 to 16.4) > 10–20 weeks of SLT	12.5 (0.39 to 24.6) > 20 weeks of SLT	1.2 (0.56 to 1.8) > 10–20 weeks of SLT	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 26 (3)	IPD 53 (4)	IPD 86 (3)	IPD 40 (3)	
SLT > 3 months from aphasia onset (95% CI)	9.3 (3.1 to 15.5) > 20 weeks of SLT	5.2 (2.5 to 7.9) > 20 weeks of SLT	4.1 (1.8 to 6.5) > 10–20 weeks of SLT	NS	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 14 (1)	IPD 49 (1)	IPD 33 (2)		

continued

TABLE 34 Subgroup analysis summary of greatest significant gains (95% CI) from baseline by SLT regimen and language domain, IPD (RCTs) and GRADE (continued)

SLT regimen	Overall language ability (WAB-AQ, score 0–100 points)	Auditory comprehension (TT-AAT, score 0–50 points)	Naming (BNT, score 0–60 points)	Functional communication (AAT-SSC, score 0–5 points)	GRADE rating
<i>Aphasia severity</i>					
Mild–moderate aphasia (95% CI)	10.0 (2.4 to 17.6) > 10 weeks of SLT	NS	16.0 (6.6 to 25.4) > 20 weeks of SLT	0.6 (0.1 to 1.2) 3–20 weeks of SLT	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 16 (2)		IPD 26 (2)	IPD 45 (2)	
Moderate–severe aphasia (95% CI)	23.5 (12.1 to 35.0) > 10 weeks of SLT	10.6 (3.9 to 17.3) > 20 weeks of SLT	7.5 (1.1 to 14.0) > 10–20 weeks of SLT	1.1 (0.8 to 1.5) > 20 weeks of SLT	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 18 (2)	IPD 105 (3)	IPD 71 (4)	IPD 61 (4)	
<i>Sex</i>					
Female (95% CI)	24.5 (13.2 to 35.8) > 20 weeks of SLT	7.0 (0.8 to 13.1) > 20 weeks of SLT	20.3 (9.4 to 31.2) >20 weeks of SLT	1.0 (0.1 to 1.8) > 4 weeks of SLT	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 12 (2)	IPD 63 (3)	IPD 62 (3)	IPD 16 (2)	
Male (95% CI)	16.7 (7.8 to 25.7) > 10–20 weeks of SLT	9.3 (2.9 to 15.6) > 10–20 weeks of SLT	11.0 (5.4 to 16.7) > 10–20 weeks of SLT	0.7 (0.4 to 1.0) > 10–20 weeks of SLT	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 26 (3)	IPD 58 (5)	IPD 51 (4)	IPD 46 (4)	
<i>Intensity of SLT (in weeks)</i>					
<i>Age group</i>					
Younger (≤ 65 years) (95% CI)	17.0 (10.0 to 24.0) > 9 hours SLT weekly	9.0 (5.4 to 12.6) > 9 hours SLT weekly	17.3 (8.3 to 26.4) ≤ 2 hours SLT weekly	0.9 (0.5 to 1.2) > 3–4 hours SLT weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 78 (3)	IPD 108 (4)	IPD 10 (2)	IPD 74 (5)	
Older (> 65 years) (95% CI)	16.9 (3.8 to 30.0) ≤ 2 hours SLT weekly	5.3 (0.67 to 10.0) > 9 hours SLT weekly	11.1 (1.4 to 20.8) ≤ 2 hours SLT weekly	1.0 (0.4 to 1.6) ≤ 2 hours SLT weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 37 (3)	IPD 33 (6)	IPD 8 (2)	IPD 41 (4)	

SLT regimen	Overall language ability (WAB-AQ, score 0–100 points)	Auditory comprehension (TT-AAT, score 0–50 points)	Naming (BNT, score 0–60 points)	Functional communication (AAT-SSC, score 0–5 points)	GRADE rating
<i>Time after aphasia onset</i>					
SLT ≤ 3 months from aphasia onset (95% CI)	24.3 (13.4 to 35.2) ≤ 2 hours SLT weekly	9.3 (2.1 to 16.5) > 9 hours SLT weekly	17.7 (4.0 to 31.4) ≤ 2 hours SLT weekly	1.3 (0.6 to 1.9) ≤ 2 hours SLT weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 62 (2)	IPD 20 (2)	IPD 10 (1)	IPD 57 (2)	
SLT > 3 months from aphasia onset (95% CI)	6.3 (2.2 to 10.3) > 3 to 4 hours SLT weekly	4.6 (2.4 to 6.8) > 9 hours SLT weekly	5.6 (3.6 to 7.6) > 3–4 hours SLT weekly	NS	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 25 (2)	IPD 121 (4)	IPD 27 (2)		
<i>Aphasia severity</i>					
Mild–moderate aphasia (95% CI)	8.0 (3.4 to 12.6) ≤ 2 and > 9 hours SLT weekly	NS	9.4 (4.6 to 14.3) > 3–4 and > 9 hours SLT weekly	0.6 (0.3 to 1.0) > 9 hours weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 48 (3)		IPD 19 (4)	IPD 27 (4)	
Moderate–severe aphasia (95% CI)	20.0 (10.1 to 29.9) > 3 to 4 hours SLT weekly	9.1 (2.6 to 15.6) ≤ 2 hours and > 9 hours SLT weekly	12.4 (4.3 to 20.6) ≤ 2 hours SLT weekly	0.98 (0.3 to 1.6) ≤ 3 hours weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 64 (4)	IPD 9 (2)	IPD 16 (2)	IPD 42 (3)	
<i>Sex</i>					
Female (95% CI)	18.5 (7.5 to 29.6) ≤ 2 hours SLT weekly	7.9 (1.8 to 14.0) ≤ 2 hours SLT weekly	13.5 (4.7 to 22.3) > 2–3 hours SLT weekly	1.2 (0.47 to 1.8) ≤ 2 hours SLT weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 37 (3)	IPD 10 (2)	IPD 38 (5)	IPD 39 (4)	
Male (95% CI)	15.1 (7.9 to 22.3) > 9 hours SLT weekly	7.6 (3.8 to 11.5) > 9 hours SLT weekly	15.5 (6.9 to 24.1) ≤ 2 hours SLT weekly	0.65 (0.4 to 0.89) > 3–4 hours SLT weekly	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 61 (3)	IPD 91 (6)	IPD 10 (2)	IPD 97 (5)	

continued

TABLE 34 Subgroup analysis summary of greatest significant gains (95% CI) from baseline by SLT regimen and language domain, IPD (RCTs) and GRADE (continued)

SLT regimen	Overall language ability (WAB-AQ, score 0–100 points)	Auditory comprehension (TT-AAT, score 0–50 points)	Naming (BNT, score 0–60 points)	Functional communication (AAT-SSC, score 0–5 points)	GRADE rating
<i>Dosage (in weeks)</i>					
<i>Age group</i>					
Younger ( $\leq 65$ years) (95% CI)	23.4 (13.5 to 33.3) SLT > 20–50 hours	6.1 (1.8 to 10.4) SLT > 14–50+ hours	13.5 (5.3 to 21.8) SLT $\leq 5$ and > 20–50 hours	1.1 (0.47 to 1.78) SLT > 14 to 20 hours	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 15 (3)	IPD 59 (6)	IPD 57 (5)	IPD 6 (3)	
Older (> 65 years) (95% CI)	15.95 (5.1 to 26.8) SLT > 5–50+ hours	5.8 (1.3 to 10.2) SLT > 20–50+ hours	8.3 (0.55 to 16.1) SLT > 20–50 hours	0.86 (0.36 to 1.36) SLT > 20–50 hours	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 16 (4)	IPD 34 (7)	IPD 24 (5)	IPD 31 (9)	
<i>Time after aphasia onset</i>					
SLT $\leq 3$ months from aphasia onset (95% CI)	27.5 (18.3 to 36.7) SLT > 20–50 hours	NS	20.7 (2.9 to 38.5) SLT > 20–50 hours	1.3 (0.69 to 1.8) SLT > 20–50 hours	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 27 (3)		IPD 31 (2)	IPD 31 (3)	
SLT > 3 months from aphasia onset (95% CI)	10.1 (4.2 to 16.0) SLT $\geq 50$ hours	4.2 (1.7 to 6.7) SLT $\geq 50$ hours	3.0 (0.90 to 5.1) > 20–50 hours	NS	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 15 (1)	IPD 76 (3)	IPD 50 (4)		
<i>Aphasia severity</i>					
Mild–moderate aphasia (95% CI)	8.7 (2.0 to 15.5) SLT > 20 hours	NS	13.0 (8.5 to 17.4) SLT > 100 hours	0.7 (0.2 to 1.2) SLT > 14–20 hours	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 8 (2)		IPD 11 (3)	IPD 8 (3)	
Moderate–severe aphasia (95% CI)	23.5 (13.5 to 33.5) SLT > 20–50 hours	8.9 (4.5 to 13.3) SLT $\geq 50$ hours	14.4 (2.1 to 26.8) SLT up to 5 hours	1.1 (0.8 to 1.4) SLT $\geq 50$ hours	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 23 (3)	IPD 142 (6)	IPD 28 (2)	IPD 72 (6)	

SLT regimen	Overall language ability (WAB-AQ, score 0–100 points)	Auditory comprehension (TT-AAT, score 0–50 points)	Naming (BNT, score 0–60 points)	Functional communication (AAT-SSC, score 0–5 points)	GRADE rating
Sex					
Female (95% CI)	24.4 (12.2 to 36.5) SLT > 20–50 hours	7.0 (2.9 to 11.2) SLT ≥ 50 hours	10.9 (1.96 to 19.9) SLT > 20–50 hours	1.6 (0.57 to 2.6) SLT > 4–20 hours	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 13 (2)	IPD 77 (6)	IPD 32 (5)	IPD 14 (2)	
Male (95% CI)	15.6 (6.2 to 25.0) SLT > 20–50 hours	6.5 (1.8 to 11.2) SLT > 20–50 hours	11.8 (5.1 to 18.5) SLT > 20–50 hours	0.70 (0.48 to 0.90) SLT ≥ 50 hours	Very low <sup>a</sup> for all language domains
IPD (RCTs)	IPD 18 (4)	IPD 56 (7)	IPD 49 (5)	IPD 93 (6)	
NS, not significant.					
a The evidence was downgraded for insufficient data to inform our analysis.					
<b>Note</b>					
Red text denotes > 50% relative variance and reported for completeness, but not considered in our interpretation of results.					



## Appendix 31 Risk of date of recruitment bias

In this sensitivity analysis, we considered the possibility of bias related to the age of included data sets. The oldest data set was from 1973, whereas the more recent data sets were from 2016. We took recruitment date as reported by the primary research team and, when unavailable (e.g. in some public domain data sets), we took the date of the first associated publication. Data sets were categorised as pre 2000 and post 2000. Recruitment year groups were added to the basic model of baseline score, sex, time since index event and age (see *Chapter 5*; RCT data set only) to examine whether or not there was any evidence of an effect of date of recruitment. We found no evidence that date of participant recruitment contributed to the findings in relation to overall language ability, auditory comprehension, naming or functional communication (observer rated) (*Figure 33*).

(a) Type 3 tests of fixed effects				
Effect	Number	Denominator		Pr > F
	DF	DF	F-value	
Baseline score	1	463	77.22	<0.0001
Sex	1	463	1.69	0.1944
Age group	3	463	1.33	0.2655
Time group	3	463	1.90	0.1287
Recruit group	1	463	1.00	0.3178
Recruit group	Estimate	Lower	Upper	
2000 and later	15.2463	8.9165	21.5761	IPD 111, D 4
Before 2000	10.3580	2.7439	17.9721	IPD 371, D 7

(b) Type 3 tests of fixed effects				
Effect	Number	Denominator		Pr > F
	DF	DF	F-value	
Baseline score	1	516	85.65	<0.0001
Sex	1	516	0.88	0.3486
Age group	3	516	5.81	0.0007
Time group	3	516	1.22	0.3025
Recruit group	1	516	0.31	0.5769
Recruit group	Estimate	Lower	Upper	
2000 and later	3.8970	0.7326	7.0613	IPD 82, D 3
Before 2000	1.8442	-4.4484	8.1367	IPD 458, D 13

FIGURE 33 Risk of date of recruitment bias. (a) Overall language ability; (b) auditory comprehension; (c) naming; and (d) functional communication (observer rated, activity data included). DF, degrees of freedom. (*continued*)

(c) Type 3 tests of fixed effects				
Effect	Number DF	Denominator DF	F-value	Pr > F
Baseline score	1	364	5.84	0.0162
Sex	1	364	0.04	0.8507
Age group	3	364	2.71	0.0452
Time group	3	364	1.87	0.1348
Recruit group	1	364	0.64	0.4234
Recruit group	Estimate	Lower	Upper	
2000 and later	7.8184	2.8022	12.8346	IPD 81, D 3
Before 2000	3.5121	-5.6694	12.6936	IPD 304, D 10

(d) Type 3 tests of fixed effects				
Effect	Number DF	Denominator DF	F-value	Pr > F
Baseline score	1	511	35.45	<0.0001
Sex	1	511	5.36	0.0210
Age group	3	511	1.04	0.3750
Time group	3	511	3.58	0.0139
Recruit group	1	511	0.15	0.6956
Recruit group	Estimate	Lower	Upper	
2000 and later	0.6907	0.3850	0.9965	IPD 103, D 2
Before 2000	0.5383	-0.1495	1.2262	IPD 430, D 12

FIGURE 33 Risk of date of recruitment bias. (a) Overall language ability; (b) auditory comprehension; (c) naming; and (d) functional communication (observer rated, activity data included). DF, degrees of freedom.

## Appendix 32 Risk of publication bias

We considered risk of publication bias (the risk of an imbalance in the literature towards reporting of significant findings). We were unable to use a funnel plot to explore publication bias because of the nature of the data set.

We looked at the distribution of studies, with similar numbers of participants (in age groups), and those that reported a significant finding. The analysis was restricted to 164 data sets with an associated publication and we used a chi-squared test. We found no evidence to suggest a publication bias by sample size ( $p = 0.77$ ; Table 35).

We also considered the historic nature of the data sets and whether or not there was an association between the age of a publication and the reporting of significant (or non-significant) findings. The analysis was also restricted to 164 data sets with an associated publication and we used a chi-squared test. We found evidence to suggest a publication bias by date of publication ( $p = 0.014$ ). Earlier publications had a higher proportion of non-significant results than findings reported in later publications (Table 36).

TABLE 35 Distribution of studies, by participant number (in age groups) and report of a significant finding

Sample size (group) (n participants)	Reported a significant result, n (% of total publications)	
	No	Yes
> 100	3	5 (63)
51-100	3	8 (73)
31-50	3	15 (83)
21-30	8	25 (76)
11-20	12	57 (83)
Up to 10	5	20 (80)

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TABLE 36 Association between publication age and report of significant (or non-significant) findings

Year of publication	Reported a significant result, n (% of total publications)	
	No	Yes
1973-89	7	4 (37)
1990-99	2	13 (87)
2000-4	3	16 (84)
2005-9	4	28 (88)
2010-14	15	53 (78)
2015-17	3	12 (80)



## Appendix 33 Wu–Hausman test

TABLE 37 Wu–Hausman test for fixed- vs. random-effects model

Language domain	W	W-alternative	Fixed effect ( <i>p</i> -value for data set)	Relative variability due to data set (%)
Overall language ability	0.13	0.36	< 0.0001	19.3
Auditory comprehension	3.55	-1.88	< 0.0001	24.3
Naming	0.37	-0.61	< 0.0001	41.4
Other spoken language	0.55	0.74	0.0002	16.7
Reading comprehension <sup>a</sup>	< 0.001	< 0.001	Not assessable	0
Writing	2.29	-1.51	0.06	13.8
Functional communication (observer rated)	3.49	-1.97	< 0.0001	30.8

a Based on one RCT data set.



## Appendix 34 Subgroup analysis

TABLE 38 Younger ( $\leq 65$  years) vs. older ( $> 65$  years) participant subgroups; multivariable estimates of means (95% CIs)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	Data sets (n)	IPD (n)	Estimate of mean (95% CI)
<b>Base model</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
Female	11	97	13.97 (7.98 to 19.97)	9	109	13.86 (6.92 to 20.79)
Male	11	180	12.21 (6.53 to 17.89)	10	96	11.74 (5.02 to 18.45)
0–1 month	8	97	17.89 (11.84 to 23.95)	8	163	22.36 (16.78 to 27.95)
> 1–3 months	6	45	16.44 (9.77 to 23.11)	5	19	11.71 (2.60 to 20.82)
> 3–6 months	3	10	9.52 (–1.33 to 20.36)	1	6	11.18 (–5.05 to 27.41)
> 6 months	4	125	8.53 (–0.33 to 17.39)	2	17	5.94 (–6.00 to 17.88)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
Female	16	135	4.63 (1.73 to 7.53)	13	76	4.50 (1.09 to 7.92)
Male	16	225	3.95 (1.20 to 6.69)	15	104	3.22 (0.05 to 6.38)
0–1 month	6	62	7.66 (3.49 to 11.82)	6	77	4.77 (0.70 to 8.83)
> 1–3 months	9	70	3.91 (0.54 to 7.27)	8	27	6.63 (2.22 to 11.05)
> 3–6 months	5	37	3.80 (–1.48 to 9.08)	3	24	2.54 (–3.95 to 9.03)
> 6 months	9	191	1.79 (–1.65 to 5.23)	7	52	1.50 (–2.48 to 5.48)
<i>Naming on the BNT, range 0–60</i>						
Female	13	87	9.85 (5.30 to 14.40)	11	78	4.01 (–0.96 to 8.98)
Male	13	140	7.21 (2.87 to 11.54)	12	80	7.44 (2.61 to 12.27)
0–1 month	5	55	14.61 (8.33 to 20.88)	5	74	11.56 (5.29 to 17.83)
> 1–3 months	8	65	9.15 (4.16 to 14.14)	7	28	6.68 (0.26 to 13.10)
> 3–6 months	5	44	5.21 (–1.06 to 11.47)	3	26	1.91 (–6.48 to 10.31)
> 6 months	7	63	5.15 (–0.22 to 10.52)	5	30	2.74 (–4.02 to 9.50)
<i>Functional communication (observer rated)<sup>a</sup> on the AAT-SSC, range 0–5</i>						
Female	14	109	0.79 (0.52 to 1.06)	14	127	0.69 (0.41 to 0.97)
Male	14	183	0.55 (0.29 to 0.81)	13	113	0.57 (0.30 to 0.83)
0–1 month	6	78	1.19 (0.83 to 1.55)	6	154	1.11 (0.82 to 1.39)
> 1–3 months	5	46	0.86 (0.50 to 1.22)	5	22	0.87 (0.37 to 1.36)
> 3–6 months	3	38	0.27 (–0.20 to 0.75)	3	24	0.28 (–0.27 to 0.84)
> 6 months	7	130	0.36 (0.05 to 0.67)	7	40	0.25 (–0.13 to 0.63)
<b>Frequency of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
$\leq 2$ days per week	5	62	9.24 (1.84 to 16.63)	5	28	11.75 (2.17 to 21.32)
> 2–3 days per week	2	20	13.38 (4.17 to 22.59)	1	1	7.13 (–28.53 to 42.79)
> 3–4 days per week	5	46	12.99 (4.63 to 21.34)	3	28	14.00 (4.05 to 23.96)
> 4–5 days per week	6	107	15.12 (8.15 to 22.08)	6	87	11.71 (3.68 to 19.74)

continued

TABLE 38 Younger ( $\leq 65$  years) vs. older ( $> 65$  years) participant subgroups; multivariable estimates of means (95% CIs) (continued)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	Data sets (n)	IPD (n)	Estimate of mean (95% CI)
> 5 days per week	2	22	14.23 (5.19 to 23.24)	2	10	17.19 (3.85 to 30.53)
Reference group	3	20	13.53 (4.13 to 22.93)	3	51	10.74 (1.22 to 20.26)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
$\leq 2$ days per week	4	52	-0.35 (-4.15 to 3.45)	4	12	1.92 (-3.91 to 7.76)
> 2–3 days per week	4	57	2.36 (-1.82 to 6.53)	3	32	5.06 (-0.81 to 10.94)
> 3–4 days per week	5	64	6.78 (2.33 to 11.22)	3	50	8.48 (2.04 to 14.93)
> 4–5 days per week	8	113	5.76 (2.47 to 9.04)	8	58	2.41 (-1.53 to 6.36)
> 5 days per week	3	36	3.24 (-1.26 to 7.74)	3	15	5.06 (-0.79 to 10.91)
Reference group	6	38	4.27 (0.18 to 8.36)	6	13	0.85 (-4.51 to 6.21)
<i>Naming on the BNT, range 0–60</i>						
$\leq 2$ days per week	4	26	15.02 (8.95 to 21.10)	4	16	9.83 (2.44 to 17.22)
> 2–3 days per week	3	55	7.61 (1.24 to 13.98)	2	29	6.77 (-2.71 to 16.24)
> 3–4 days per week	4	54	9.24 (2.66 to 15.83)	2	49	7.79 (-2.54 to 18.11)
> 4–5 days per week	6	54	5.66 (0.45 to 10.86)	6	50	1.82 (-4.41 to 8.04)
> 5 days per week		0	-		0	-
Reference group	5	38	8.43 (3.26 to 13.59)	5	14	8.54 (1.10 to 15.99)
<i>Functional communication (observer rated)<sup>a</sup> on the AAT-SSC, range 0–5</i>						
$\leq 2$ days per week	5	57	0.49 (0.16 to 0.83)	5	25	0.60 (0.06 to 1.12)
> 2–3 days per week	3	64	0.55 (0.18 to 0.92)	3	28	0.57 (-0.08 to 1.23)
> 3–4 days per week	4	48	0.73 (0.31 to 1.15)	3	54	0.78 (0.15 to 1.40)
> 4–5 days per week	9	72	0.85 (0.54 to 1.15)	8	83	0.69 (0.30 to 1.08)
> 5 days per week	2	3	1.18 (0.28 to 2.08)	3	6	0.43 (-0.53 to 1.39)
Reference group	6	45	0.32 (-0.02 to 0.65)	6	40	0.58 (0.11 to 1.06)
<i>Duration of SLT</i>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
$\leq 2$ weeks	2	32	2.97 (-4.89 to 10.82)	2	18	11.24 (-3.17 to 25.67)
3 weeks	3	105	12.67 (7.75 to 17.60)	2	53	10.88 (-0.19 to 21.94)
4–10 weeks	4	60	12.53 (7.11 to 17.94)	4	18	8.67 (-3.39 to 20.73)
> 10–20 weeks	3	25	22.69 (15.20 to 30.19)	3	20	12.92 (1.15 to 24.69)
> 20 weeks	2	19	14.58 (6.75 to 22.41)	2	15	20.60 (7.77 to 33.42)
Reference group	2	15	17.52 (8.65 to 26.39)	2	50	9.95 (-1.45 to 21.36)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
$\leq 2$ weeks	6	47	7.26 (1.03 to 13.50)	6	46	3.04 (-1.78 to 7.85)
3 weeks	2	95	3.92 (-4.50 to 12.35)	1	10	0.71 (-8.48 to 9.90)
4–10 weeks	2	58	1.87 (-6.46 to 10.20)	3	10	1.51 (-6.08 to 9.10)
> 10–20 weeks	5	60	8.41 (2.62 to 14.20)	5	33	4.66 (-0.21 to 9.53)
> 20 weeks	3	67	-7.08 (-14.64 to 0.48)	3	69	5.96 (-0.24 to 12.15)
Reference group	5	33	7.53 (1.61 to 13.45)	5	12	0.69 (-5.39 to 6.78)

TABLE 38 Younger ( $\leq 65$  years) vs. older ( $> 65$  years) participant subgroups; multivariable estimates of means (95% CIs) (continued)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	Data sets (n)	IPD (n)	Estimate of mean (95% CI)
<i>Naming on the BNT, range 0–60</i>						
$\leq 4$ weeks	5	49	6.62 (0.24 to 12.99)	4	37	2.79 (-5.95 to 11.52)
4–10 weeks	3	18	7.34 (-1.49 to 16.16)	3	9	4.56 (-5.64 to 14.75)
$> 10$ –20 weeks	4	59	11.27 (5.44 to 17.11)	4	27	3.03 (-4.92 to 10.97)
$> 20$ weeks	3	63	8.60 (1.25 to 15.96)	3	71	11.23 (2.03 to 20.43)
Reference group	5	38	9.50 (3.63 to 15.36)	5	14	5.47 (-2.92 to 13.86)
<i>Functional communication (observer rated)<sup>a</sup> on the AAT-SSC, range 0–5</i>						
$\leq 3$ weeks	4	27	0.37 (-0.12 to 0.87)	4	28	0.30 (-0.17 to 0.77)
3 weeks	2	27	1.20 (0.63 to 1.77)	2	29	0.31 (-0.22 to 0.83)
4–10 weeks	2	48	1.16 (0.57 to 1.76)	2	9	1.32 (0.51 to 2.13)
$> 10$ –20 weeks	4	54	0.66 (0.26 to 1.05)	4	22	0.63 (0.15 to 1.11)
$> 20$ weeks	4	72	0.70 (0.25 to 1.14)	4	78	0.76 (0.43 to 1.09)
Reference group	5	40	0.28 (-0.11 to 0.67)	5	39	0.36 (-0.09 to 0.81)
<i>Intensity of SLT</i>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
$\leq 2$ hours weekly	3	37	13.41 (4.98 to 21.84)	3	37	16.92 (3.80 to 30.04)
$> 2$ –3 hours weekly	7	70	10.46 (3.78 to 17.14)	6	23	10.13 (-0.47 to 20.73)
$> 3$ –4 hours weekly	4	39	14.75 (6.77 to 22.72)	3	65	14.78 (4.56 to 25.01)
$> 4$ –9 hours weekly	2	38	12.68 (4.70 to 20.65)	2	12	12.20 (-3.64 to 28.04)
$> 9$ hours weekly	3	78	16.97 (9.96 to 23.98)	3	18	11.46 (-0.05 to 22.96)
Reference group	2	15	15.60 (5.40 to 25.79)	2	50	13.22 (2.07 to 24.37)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
$\leq 2$ hours weekly	2	15	8.15 (2.67 to 13.63)	2	4	5.11 (-3.58 to 13.79)
$> 2$ –3 hours weekly	7	81	0.43 (-3.42 to 4.28)	6	39	3.00 (-1.64 to 7.63)
$> 3$ –4 hours weekly	3	46	6.38 (1.04 to 11.72)	2	66	7.03 (-0.08 to 14.14)
$> 4$ –9 hours weekly	5	77	4.05 (0.25 to 7.85)	5	26	1.50 (-3.73 to 6.74)
$> 9$ hours weekly	4	108	8.96 (5.35 to 12.56)	6	33	5.34 (0.67 to 10.02)
Reference group	5	33	4.38 (-0.07 to 8.84)	5	12	0.22 (-5.55 to 5.99)
<i>Naming on the BNT, range 0–60</i>						
$\leq 2$ hours weekly	2	10	17.35 (8.32 to 26.38)	2	8	11.12 (1.41 to 20.82)
$> 2$ –3 hours weekly	5	71	7.92 (1.72 to 14.12)	4	30	7.57 (-0.61 to 15.75)
$> 3$ –4 hours weekly	3	54	10.38 (3.18 to 17.59)	3	73	5.75 (-2.61 to 14.12)
$> 4$ –9 hours weekly	2	28	5.43 (-2.57 to 13.42)	2	13	1.92 (-9.87 to 13.71)
$> 9$ hours weekly	4	26	6.15 (-0.59 to 12.89)	4	20	2.98 (-4.76 to 10.73)
Reference group	5	38	8.42 (2.57 to 14.28)	5	14	8.24 (0.43 to 16.05)

continued

TABLE 38 Younger ( $\leq 65$  years) vs. older ( $> 65$  years) participant subgroups; multivariable estimates of means (95% CIs) (continued)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	Data sets (n)	IPD (n)	Estimate of mean (95% CI)
<i>Functional communication (observer rated)<sup>a</sup> on the AAT-SSC, range 0–5</i>						
$\leq 2$ hours weekly	4	42	0.61 (0.22 to 1.01)	4	41	0.97 (0.38 to 1.57)
$> 2$ –3 hours weekly	4	43	0.78 (0.36 to 1.21)	5	31	0.61 (0.05 to 1.17)
$> 3$ –4 hours weekly	5	74	0.87 (0.53 to 1.22)	4	104	0.61 (0.17 to 1.06)
$> 4$ –9 hours weekly	2	52	0.48 (0.12 to 0.84)	2	7	0.41 (–0.51 to 1.34)
$> 9$ hours weekly	6	41	0.74 (0.39 to 1.09)	6	19	0.64 (0.05 to 1.23)
Reference group	5	40	0.29 (–0.06 to 0.64)	5	39	0.54 (0.04 to 1.04)
<b>Dosage of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
$\leq 5$ hours	5	69	8.68 (2.45 to 14.90)	6	32	8.60 (–0.36 to 17.57)
$> 5$ –14 hours	4	61	12.87 (6.48 to 19.27)	3	53	13.90 (4.79 to 23.08)
$> 14$ –20 hours	4	67	13.34 (7.13 to 19.56)	3	22	14.90 (4.09 to 25.70)
$> 20$ – $< 50$ hours	3	15	23.38 (13.47 to 33.28)	4	16	15.95 (5.08 to 26.83)
$\geq 50$ hours	4	40	14.82 (7.24 to 22.39)	4	28	14.51 (5.29 to 23.73)
Reference group	4	24	12.88 (4.96 to 20.80)	4	53	10.37 (0.85 to 19.89)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
$\leq 5$ hours	3	50	0.93 (–3.73 to 5.60)	3	14	–1.08 (–7.91 to 5.75)
$> 5$ –14 hours	4	57	2.36 (–2.15 to 6.87)	3	27	1.38 (–4.38 to 7.13)
$> 14$ –20 hours	2	61	5.04 (0.36 to 9.73)	1	5	2.44 (–6.18 to 11.07)
$> 20$ – $< 50$ hours	6	59	6.06 (1.75 to 10.36)	7	34	5.80 (1.35 to 10.24)
$\geq 50$ hours	6	95	4.51 (0.06 to 8.96)	6	88	5.61 (1.67 to 9.54)
Reference group	6	38	4.89 (0.51 to 9.26)	6	13	1.49 (–4.08 to 7.07)
<i>Naming on the BNT, range 0–60</i>						
$\leq 5$ hours	2	17	13.24 (1.35 to 25.12)	2	11	–2.06 (–16.15 to 12.04)
$> 5$ –20 hours	4	37	4.44 (–4.66 to 13.54)	2	24	5.93 (–4.91 to 16.77)
$> 20$ – $< 50$ hours	5	57	13.56 (5.30 to 21.79)	5	24	8.32 (0.55 to 16.08)
$50$ – $< 100$ hours	2	55	9.06 (–5.74 to 23.87)	2	67	5.96 (–4.96 to 16.89)
$\geq 100$ hours	3	23	–2.15 (–13.10 to 8.80)	3	18	5.12 (–3.39 to 13.63)
Reference group	5	38	11.38 (3.13 to 19.62)	5	14	8.96 (0.59 to 17.33)
<i>Functional communication (observer rated)<sup>a</sup> on the AAT-SSC, range 0–5</i>						
$\leq 5$ hours	2	34	0.53 (0.12 to 0.95)	3	13	–0.13 (–0.81 to 0.56)
$> 5$ –14 hours	5	47	0.61 (0.28 to 0.95)	5	57	0.78 (0.30 to 1.26)
$> 14$ –20 hours	3	6	1.12 (0.47 to 1.78)	1	5	0.75 (–0.27 to 1.76)
$> 20$ – $< 50$ hours	7	65	0.50 (0.21 to 0.80)	9	31	0.86 (0.36 to 1.36)
$\geq 50$ hours	6	87	0.96 (0.66 to 1.25)	7	88	0.64 (0.20 to 1.08)
Reference group	7	49	0.19 (–0.10 to 0.48)	7	42	0.53 (0.04 to 1.02)
–, Insufficient data.						
a Including TOMs activity data.						
Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.						

TABLE 39 Earlier ( $\leq 3$  months) vs. later ( $> 3$  months) since aphasia onset subgroup analysis; multivariable estimates of means (95% CIs)

	Early ( $\leq 3$ months)			Late ( $> 3$ months)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<b>Base model</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
Female	10	150	21.54 (15.70 to 27.38)	4	56	13.86 (6.92 to 20.79)
Male	10	174	17.99 (12.35 to 23.64)	4	102	11.74 (5.02 to 18.45)
$\leq 55$ years	10	55	21.13 (14.30 to 27.96)	4	81	6.98 (4.30 to 9.65)
56–65 years	10	87	18.98 (12.73 to 25.23)	3	54	4.13 (1.06 to 7.19)
66–75 years	9	76	18.60 (12.15 to 25.05)	2	20	2.70 (–1.67 to 7.06)
$> 75$ years	6	106	20.35 (13.86 to 26.85)	1	3	5.33 (–5.08 to 15.73)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
Female	11	112	4.00 (–0.78 to 8.79)	10	99	2.58 (0.50 to 4.66)
Male	11	124	3.36 (–1.41 to 8.12)	11	205	1.93 (0.11 to 3.75)
$\leq 55$ years	10	53	7.12 (1.93 to 12.30)	9	125	4.03 (2.06 to 6.01)
56–65 years	11	79	2.51 (–2.37 to 7.39)	9	103	1.80 (–0.27 to 3.86)
66–75 years	9	59	4.12 (–1.05 to 9.29)	9	57	1.37 (–0.95 to 3.70)
$> 75$ years	7	45	0.97 (–4.41 to 6.35)	6	19	1.82 (–1.70 to 5.33)
<i>Naming on the BNT, range 0–60</i>						
Female	9	104	9.29 (1.49 to 17.09)	8	61	2.20 (0.58 to 3.82)
Male	9	118	9.35 (1.60 to 17.10)	9	102	1.26 (–0.20 to 2.73)
$\leq 55$ years	8	44	13.30 (4.93 to 21.66)	8	59	3.28 (1.68 to 4.88)
56–65 years	9	76	9.20 (1.33 to 17.07)	7	48	2.23 (0.41 to 4.05)
66–75 years	7	58	8.18 (–0.06 to 16.41)	7	39	1.17 (–0.71 to 3.05)
$> 75$ years	6	44	6.60 (–1.87 to 15.08)	6	17	0.24 (–2.44 to –2.92)
<i>Functional communication observer rated<sup>a</sup> on the AAT-SSC, range 0–5</i>						
Female	8	151	1.12 (0.77 to 1.48)	8	86	0.37 (–0.06 to 0.69)
Male	8	149	0.93 (0.57 to 1.29)	9	147	0.14 (–0.23 to 0.51)
$\leq 55$ years	7	53	1.15 (0.73 to 1.58)	8	94	0.29 (–0.09 to 0.67)
56–65 years	8	71	1.05 (0.65 to 1.44)	7	74	0.25 (–0.14 to 0.64)
66–75 years	7	79	0.89 (0.49 to 1.28)	9	43	0.14 (–0.26 to 0.54)
$> 75$ years	7	97	1.02 (0.63 to 1.42)	6	22	0.23 (–0.23 to 0.69)
<b>Frequency of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
$\leq 2$ days per week	4	56	15.88 (7.00 to 24.75)	2	34	2.37 (–2.54 to 7.28)
$> 2$ –3 days per week	1	3	27.75 (–3.56 to 51.93)	2	18	2.52 (–3.12 to 8.16)
$> 3$ –4 days per week	4	41	19.24 (7.71 to 30.76)	3	33	5.06 (0.90 to 9.22)
$> 4$ –5 days per week	5	150	21.42 (13.45 to 29.39)	1	44	6.32 (1.58 to 11.07)
$> 5$ days per week	1	9	18.35 (3.23 to 33.47)	1	23	5.41 (0.04 to 10.77)
Reference group	2	65	19.53 (10.30 to 28.76)	1	6	2.41 (–5.78 to 10.59)

continued

TABLE 39 Earlier ( $\leq 3$  months) vs. later ( $> 3$  months) since aphasia onset subgroup analysis; multivariable estimates of means (95% CIs) (continued)

	Early ( $\leq 3$ months)			Late ( $> 3$ months)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<i>Auditory comprehension on the TT-AAT, range 0-50</i>						
$\leq 2$ days per week	3	27	-1.80 (-8.77 to 5.16)	2	37	0.13 (-2.92 to 3.19)
$> 2-3$ days per week	3	10	0.81 (-8.66 to 10.27)	4	79	1.78 (-0.82 to 4.39)
$> 3-4$ days per week	3	87	7.47 (-2.22 to 17.17)	3	27	3.49 (0.16 to 6.82)
$> 4-5$ days per week	5	82	4.70 (-1.61 to 11.02)	5	89	3.71 (1.41 to 6.00)
$> 5$ days per week	1	7	0.17 (-9.77 to 10.11)	2	44	2.76 (-0.21 to 5.73)
Reference group	3	23	4.61 (-2.54 to 11.76)	4	28	-0.76 (-3.86 to 2.35)
<i>Naming on the BNT, range 0-60</i>						
$\leq 2$ days per week	3	33	16.96 (7.68 to 26.24)	2	9	3.26 (-0.79 to 7.30)
$> 2-3$ days per week	2	6	-0.99 (-15.84 to 13.86)	3	78	2.81 (0.60 to 5.02)
$> 3-4$ days per week	3	83	9.44 (-3.29 to 22.18)	2	20	1.04 (-2.08 to 4.17)
$> 4-5$ days per week	5	85	8.67 (0.11 to 17.23)	3	19	1.55 (-1.48 to 4.59)
$> 5$ days per week	-	-	-	-	-	-
Reference group	2	15	15.86 (5.15 to 26.57)	4	37	0.02 (-2.14 to 2.18)
<i>Functional communication observer rated<sup>d</sup> on the AAT-SSC, range 0-5</i>						
$\leq 2$ days per week	3	43	0.89 (0.37 to 1.41)	2	39	0.07 (-0.36 to 0.51)
$> 2-3$ days per week	1	3	0.41 (-1.09 to 1.91)	3	90	0.20 (-0.20 to 0.61)
$> 3-4$ days per week	1	80	1.55 (0.59 to 2.52)	3	22	0.16 (-0.31 to 0.63)
$> 4-5$ days per week	5	119	1.11 (0.67 to 1.54)	6	36	0.36 (-0.05 to 0.77)
$> 5$ days per week	1	5	0.61 (-0.45 to 1.67)	2	4	0.62 (-0.15 to 1.38)
Reference group	3	50	0.77 (0.26 to 1.28)	4	35	0.002 (-0.40 to 0.41)
<i>Duration of SLT</i>						
<i>Overall language ability on the WAB-AQ, range 0-100</i>						
$\leq 2$ weeks	2	50	11.15 (-0.70 to 23.01)	0	0	-
3 weeks	2	69	19.37 (9.23 to 29.51)	2	89	3.22 (-1.64 to 8.07)
4-10 weeks	3	26	24.73 (12.53 to 36.92)	3	52	0.88 (-4.21 to 5.96)
$> 10-20$ weeks	3	42	22.45 (12.85 to 32.05)	1	3	6.90 (-5.32 to 19.12)
$> 20$ weeks	2	20	21.96 (10.47 to 33.46)	1	14	9.30 (3.12 to 15.48)
Reference group	2	65	19.51 (9.58 to 29.44)	0	0	-
<i>Auditory comprehension on the TT-AAT, range 0-50</i>						
$\leq 2$ weeks	3	56	3.04 (-6.29 to 12.36)	4	37	3.69 (1.04 to 6.34)
3 weeks	1	11	8.33 (-11.40 to 28.06)	2	94	3.30 (1.05 to 5.56)
4-10 weeks	1	7	-6.40 (-26.57 to 13.76)	3	61	1.61 (-0.76 to 3.98)
$> 10-20$ weeks	4	53	8.81 (1.23 to 16.39)	3	41	2.40 (-0.10 to 4.89)
$> 20$ weeks	3	87	-3.52 (-12.34 to 5.30)	1	49	5.20 (2.52 to 7.88)
Reference group	3	23	9.89 (1.85 to 17.93)	3	22	-2.54 (-5.66 to 0.58)

TABLE 39 Earlier ( $\leq 3$  months) vs. later ( $> 3$  months) since aphasia onset subgroup analysis; multivariable estimates of means (95% CIs) (continued)

	Early ( $\leq 3$ months)			Late ( $> 3$ months)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<b>Naming on the BNT, range 0–60</b>						
$\leq 4$ weeks	3	61	5.17 (–8.86 to 19.20)	4	25	1.54 (–0.99 to 4.08)
4–10 weeks	1	7	4.95 (–20.49 to 30.39)	3	20	1.48 (–1.04 to 4.00)
$> 10$ –20 weeks	3	53	11.81 (–0.10 to 23.72)	2	33	4.12 (1.79 to 6.45)
$> 20$ weeks	3	86	12.50 (0.39 to 24.61)	1	48	1.89 (–0.59 to 4.37)
Reference group	2	15	15.56 (1.92 to 29.20)	4	37	0.48 (–1.47 to 2.44)
<b>Functional communication observer rated<sup>a</sup> on the AAT-SSC, range 0–5</b>						
$\leq 2$ weeks	1	29	0.76 (–0.42 to 1.95)	4	26	0.08 (–0.43 to 0.59)
3 weeks	1	35	0.94 (0.17 to 1.72)	1	21	0.41 (–0.29 to 1.11)
4–10 weeks		0	–	2	57	0.47 (–0.17 to 1.11)
$> 10$ –20 weeks	3	40	1.16 (0.56 to 1.77)	2	36	0.17 (–0.39 to 0.73)
$> 20$ weeks	3	94	1.08 (0.41 to 1.74)	2	57	0.36 (–0.32 to 1.03)
Reference group	3	50	0.77 (0.10 to 1.43)	3	29	–0.06 (–0.58 to 0.46)
<b>Intensity of SLT</b>						
<b>Overall language ability on the WAB-AQ, range 0–100</b>						
$\leq 2$ hours weekly	2	62	24.27 (13.37 to 35.18)	1	12	3.27 (–2.75 to 9.30)
$> 2$ –3 hours weekly	4	75	16.33 (8.79 to 23.87)	3	18	0.24 (–5.05 to 5.53)
$> 3$ –4 hours weekly	3	79	24.14 (15.22 to 33.06)	2	25	6.25 (2.19 to 10.32)
$> 4$ –9 hours weekly	1	21	15.06 (–3.04 to 33.16)	1	29	2.87 (–1.81 to 7.56)
$> 9$ hours weekly	2	22	20.32 (9.79 to 30.85)	1	74	5.83 (1.97 to 9.69)
Reference group	2	65	22.27 (13.06 to 31.47)	0	0	–
<b>Auditory comprehension on the TT-AAT, range 0–50</b>						
$\leq 2$ hours weekly	1	7	6.72 (–2.55 to 15.99)	1	12	4.27 (–0.19 to 8.74)
$> 2$ –3 hours weekly	6	42	0.63 (–5.27 to 6.53)	5	78	2.13 (–0.35 to 4.60)
$> 3$ –4 hours weekly	2	104	9.19 (–0.66 to 19.04)	2	8	1.09 (–4.15 to 6.34)
$> 4$ –9 hours weekly	3	40	0.43 (–6.81 to 7.66)	3	63	1.50 (–1.02 to 4.01)
$> 9$ hours weekly	2	20	9.26 (2.04 to 16.47)	4	121	4.60 (2.43 to 6.77)
Reference group	3	23	5.06 (–1.72 to 11.84)	3	22	–2.12 (–5.51 to 1.28)
<b>Naming on the BNT, range 0–60</b>						
$\leq 2$ hours weekly	1	10	17.66 (3.95 to 31.36)	1	8	3.68 (0.11 to 7.26)
$> 2$ –3 hours weekly	5	41	8.14 (–2.83 to 19.12)	3	60	1.33 (–0.08 to 2.73)
$> 3$ –4 hours weekly	2	100	9.02 (–9.00 to 27.05)	2	27	5.58 (3.56 to 7.60)
$> 4$ –9 hours weekly	2	34	11.80 (–2.02 to 25.61)	1	7	0.55 (–3.33 to 4.43)
$> 9$ hours weekly	2	22	2.82 (–9.19 to 14.82)	2	24	2.05 (–0.17 to 4.27)
Reference group	2	15	14.39 (1.91 to 26.87)	4	37	0.75 (–0.94 to 2.44)

continued

TABLE 39 Earlier ( $\leq 3$  months) vs. later ( $> 3$  months) since aphasia onset subgroup analysis; multivariable estimates of means (95% CIs) (continued)

	Early ( $\leq 3$ months)			Late ( $> 3$ months)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<i>Functional communication observer rated<sup>a</sup> on the AAT-SSC, range 0–5</i>						
$\leq 2$ hours weekly	2	57	1.29 (0.64 to 1.95)	2	26	0.23 (–0.28 to 0.73)
$> 2$ –3 hours weekly	3	18	1.23 (0.58 to 1.88)	3	56	0.24 (–0.31 to 0.78)
$> 3$ –4 hours weekly	3	144	1.04 (0.60 to 1.48)	3	34	0.35 (–0.14 to 0.83)
$> 4$ –9 hours weekly	1	14	0.57 (–0.23 to 1.37)	2	45	0.13 (–0.31 to 0.58)
$> 9$ hours weekly	2	17	1.17 (0.49 to 1.85)	4	43	0.29 (–0.14 to 0.72)
Reference group	3	50	0.73 (0.27 to 1.19)	3	29	0.05 (–0.42 to 0.52)
<b>Dosage of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
$\leq 5$ hours	5	65	14.35 (6.74 to 21.96)	2	36	0.95 (–4.14 to 6.04)
$> 5$ –14 hours	3	69	23.58 (15.93 to 31.23)	2	45	3.20 (–1.81 to 8.22)
$> 14$ –20 hours	3	37	23.09 (14.11 to 32.08)	2	52	3.82 (–1.01 to 8.65)
$> 20$ –50 hours	3	27	27.52 (18.32 to 36.71)	2	4	–0.22 (–9.51 to 9.08)
$\geq 50$ hours	4	53	19.08 (11.32 to 26.84)	1	15	10.11 (4.22 to 16.00)
Reference group	3	71	19.44 (11.76 to 27.11)	1	6	1.05 (–7.21 to 9.32)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
$\leq 5$ hours	2	25	0.92 (–9.56 to 11.41)	2	39	–0.48 (–3.67 to 2.70)
$> 5$ –14 hours	3	38	–0.96 (–9.10 to 7.18)	3	48	1.35 (–1.72 to 4.43)
$> 14$ –20 hours	1	11	8.75 (–7.38 to 24.89)	2	55	3.39 (0.46 to 6.32)
$> 20$ –50 hours	3	32	4.60 (–2.50 to 11.70)	6	58	2.78 (0.43 to 5.12)
$\geq 50$ hours	4	107	4.84 (–2.20 to 11.88)	3	76	4.17 (1.68 to 6.66)
Reference group	3	23	6.00 (–1.14 to 13.15)	4	28	–1.26 (–4.21 to 1.69)
<i>Naming on the BNT, range 0–60</i>						
$\leq 5$ hours	2	25	13.43 (–4.74 to 31.59)	1	3	0.28 (–6.16 to 6.72)
$> 5$ –20 hours	3	43	0.06 (–16.34 to 16.46)	4	18	1.40 (–1.52 to 4.32)
$> 20$ –50 hours	2	31	20.67 (2.87 to 38.47)	4	50	3.02 (0.90 to 5.15)
$> 50$ –100 hours	2	74	8.54 (–13.30 to 30.39)	1	48	1.75 (–1.36 to 4.86)
$\geq 100$ hours	2	34	6.29 (–11.67 to 24.25)	1	7	2.42 (–2.12 to 6.96)
Reference group	2	15	21.31 (2.90 to 39.71)	4	37	0.30 (–1.85 to 2.46)
<i>Functional communication observer rated<sup>a</sup> on the AAT-SSC, range 0–5</i>						
$\leq 5$ hours	2	10	0.08 (–0.68 to 0.84)	1	37	0.05 (–0.48 to 0.58)
$> 5$ –14 hours	3	73	1.22 (0.71 to 1.73)	3	31	0.01 (–0.50 to 0.51)
$> 14$ –20 hours	1	8	1.24 (0.40 to 2.08)	2	3	0.62 (–0.27 to 1.50)
$> 20$ –50 hours	3	31	1.25 (0.69 to 1.81)	7	65	0.30 (–0.10 to 0.70)
$\geq 50$ hours	5	120	0.99 (0.49 to 1.48)	3	55	0.37 (–0.22 to 0.96)
Reference group	4	56	0.76 (0.26 to 1.26)	4	35	0.03 (–0.41 to 0.46)

–, Insufficient data.

<sup>a</sup> Observer-rated, including TOMs activity data.

Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.

TABLE 40 Severe vs. mild aphasia RCT participant subgroups; multivariable estimates of means (95% CIs)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<b>Base model</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
<b>Below the median: &lt; 64.9 (n = 319)</b>			<b>Above the median: ≥ 64.9 (n = 163)</b>			
Female	11	138	17.81 (11.13 to 24.50)	9	68	5.95 (1.36 to 10.55)
Male	11	181	14.66 (8.17 to 21.15)	10	95	6.87 (2.34 to 11.40)
≤ 55 years	11	76	19.60 (12.49 to 26.71)	9	60	7.50 (2.8 to 12.19)
56–65 years	11	91	13.99 (6.93 to 21.06)	6	50	8.36 (3.61 to 13.12)
66–75 years	10	71	14.23 (6.94 to 21.53)	7	25	5.66 (0.52 to 10.80)
> 75 years	7	81	17.13 (9.33 to 24.93)	6	28	4.11 (–1.04 to 9.26)
0–1 month	7	199	24.10 (17.62 to 30.59)	7	61	10.95 (6.18 to 15.73)
> 1–3 months	6	46	22.15 (14.43 to 29.86)	3	18	5.21 (–0.68 to 11.10)
> 3–6 months	3	10	9.25 (–4.43 to 22.93)	2	6	5.54 (–1.71 to 12.79)
> 6 months	4	64	9.45 (–2.25 to 21.16)	4	78	3.94 (–2.19 to 10.06)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
<b>Below the median: &lt; 35 (n = 395)</b>			<b>Above the median: ≥ 35 (n = 145)</b>			
Female	16	155	5.40 (2.11 to 8.69)	12	56	0.65 (–3.83 to 5.13)
Male	16	240	5.59 (2.37 to 8.83)	12	89	–1.24 (–5.61 to 3.13)
≤ 55 years	15	133	8.22 (4.90 to 11.56)	9	45	1.50 (–3.24 to 6.22)
56–65 years	16	132	5.33 (1.99 to 8.68)	13	50	–1.24 (–5.75 to 3.28)
66–75 years	15	88	5.21 (1.70 to 8.73)	9	28	–0.46 (–5.28 to 4.37)
> 75 years	11	42	3.20 (–0.80 to 7.20)	8	22	–0.98 (–5.94 to 3.97)
0–1 month	6	88	8.63 (4.51 to 12.75)	5	51	–0.12 (–5.82 to 5.59)
> 1–3 months	9	80	6.72 (3.11 to 10.32)	5	17	0.21 (–5.52 to 5.93)
> 3–6 months	4	50	4.37 (–1.43 to 10.17)	4	11	–1.77 (–8.08 to 4.54)
> 6 months	9	177	2.25 (–1.49 to 5.99)	8	66	0.50 (–4.79 to 5.79)
<i>Naming on the BNT, range 0–60</i>						
<b>Below the median: &lt; 23 (n = 304)</b>			<b>Above the median: ≥ 23 (n = 81)</b>			
Female	12	130	6.84 (1.98 to 11.71)	8	35	7.59 (3.79 to 11.38)
Male	13	174	6.99 (2.27 to 11.70)	8	46	8.36 (4.57 to 12.14)
≤ 55 years	12	79	9.53 (4.50 to 14.56)	7	24	8.79 (4.59 to 13.00)
56–65 years	12	97	7.39 (2.38 to 12.39)	7	27	8.13 (4.05 to 12.21)
66–75 years	12	84	6.76 (1.67 to 11.84)	6	13	6.74 (1.66 to 11.82)
> 75 years	9	44	3.98 (–1.59 to 9.56)	6	17	8.22 (3.43 to 13.02)
0–1 month	5	99	12.22 (6.35 to 18.09)	3	30	11.61 (6.25 to 16.97)
> 1–3 months	8	78	7.99 (2.67 to 13.30)	3	15	9.37 (3.76 to 14.97)
> 3–6 months	6	62	3.56 (–3.10 to 10.21)	2	8	6.83 (0.32 to 13.33)
> 6 months	7	65	3.89 (–1.81 to 9.59)	5	28	4.08 (–0.37 to 8.54)

continued

TABLE 40 Severe vs. mild aphasia RCT participant subgroups; multivariable estimates of means (95% CIs) (continued)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<i>Functional communication on the AAT-SSC,<sup>a</sup> range 0–5</i>						
<b>Below the median (moderate-severe): &lt; 2 (n = 280)</b>				<b>Above the median (mild-moderate): ≥ 2 (n = 253)</b>		
Female	121	14	0.88 (0.59 to 1.16)	116	12	0.54 (0.27 to 0.82)
Male	159	14	0.63 (0.36 to 0.89)	137	12	0.52 (0.24 to 0.79)
≤ 55 years	74	10	0.80 (0.47 to 1.12)	73	12	0.58 (0.29 to 0.87)
56 to 65 years	73	11	0.80 (0.47 to 1.12)	72	12	0.52 (0.23 to 0.81)
66 to 75 years	66	14	0.60 (0.27 to 0.93)	56	12	0.51 (0.21 to 0.81)
> 75 years	67	12	0.81 (0.47 to 1.16)	52	9	0.51 (0.19 to 0.82)
0–1 month	131	6	1.41 (1.07 to 1.75)	101	6	0.86 (0.53 to 1.19)
> 1–3 months	43	4	0.83 (0.41 to 1.24)	25	5	0.81 (0.44 to 1.18)
> 3–6 months	20	3	0.40 (-1.16 to 0.97)	43	3	0.14 (-0.34 to 0.62)
> 6 months	86	7	0.37 (0.04 to 0.69)	84	5	0.31 (-0.08 to 0.69)
<b>Frequency of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
<b>Below the median: &lt; 64.9 (n = 319)</b>				<b>Above the median: ≥ 64.9 (n = 163)</b>		
≤ 2 days per week	5	62	11.18 (2.38 to 19.98)	4	28	7.21 (2.13 to 12.29)
> 2–3 days per week	2	10	17.48 (3.43 to 31.53)	2	11	3.57 (-2.35 to 9.49)
> 3–4 days per week	5	38	18.25 (8.04 to 28.46)	4	36	5.42 (0.11 to 10.73)
> 4–5 days per week	5	145	17.47 (9.18 to 25.75)	5	49	6.30 (1.59 to 11.01)
> 5 days per week	2	16	16.08 (4.01 to 28.16)	2	16	9.85 (4.37 to 15.33)
Reference group	3	48	13.65 (3.37 to 23.94)	3	23	8.08 (2.74 to 13.43)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
<b>Below the median: &lt; 35 (n = 395)</b>				<b>Above the median: ≥ 35 (n = 145)</b>		
≤ 2 days per week	4	37	2.93 (-1.38 to 7.23)	3	27	-2.63 (-7.87 to 2.62)
> 2–3 days per week	3	72	3.49 (-1.03 to 8.00)	3	17	-1.64 (-7.71 to 4.44)
> 3–4 days per week	5	80	8.48 (3.67 to 13.28)	3	34	0.90 (-5.48 to 7.27)
> 4–5 days per week	8	134	5.88 (2.31 to 9.45)	6	37	1.03 (-3.96 to 6.03)
> 5 days per week	3	37	6.01 (1.17 to 10.86)	3	14	-2.17 (-7.80 to 3.46)
Reference group	6	35	4.46 (0.10 to 8.82)	5	16	-0.19 (-5.60 to 5.22)
<i>Naming on the BNT, range 0–60</i>						
<b>Below the median: &lt; 23 (n = 304)</b>				<b>Above the median: ≥ 23 (n = 81)</b>		
≤ 2 days per week	4	36	13.07 (6.99 to 19.14)	3	6	7.36 (0.56 to 14.16)
> 2–3 days per week	3	77	6.17 (-0.66 to 13.00)	1	7	10.53 (2.88 to 18.18)
> 3–4 days per week	4	58	8.18 (0.20 to 16.17)	3	45	5.96 (1.92 to 10.01)
> 4–5 days per week	6	93	3.78 (-1.61 to 9.16)	3	11	11.11 (5.61 to 16.60)
> 5 days per week	-	-	-	-	-	-
Reference group	5	40	7.72 (2.16 to 13.28)	4	12	7.51 (2.17 to 12.86)

TABLE 40 Severe vs. mild aphasia RCT participant subgroups; multivariable estimates of means (95% CIs) (continued)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<i>Functional communication on the AAT-SSC,<sup>a</sup> range 0–5</i>						
<b>Below the median (moderate–severe): &lt; 2 (n = 280)</b>			<b>Above the median (mild–moderate): ≥ 2 (n = 251)</b>			
≤ 2 days per week	38	5	0.52 (0.08 to 0.97)	44	5	–0.52 (0.21 to 0.83)
> 2–3 days per week	27	3	0.84 (0.31 to 1.38)	66	3	0.34 (0.01 to 0.68)
> 3–4 days per week	55	2	1.00 (0.48 to 1.51)	47	3	0.58 (0.18 to 0.99)
> 4–5 days per week	100	9	0.78 (0.47 to 1.09)	55	8	0.66 (0.36 to 0.96)
> 5 days per week	1	1	1.06 (–1.06 to 3.18)	8	3	0.63 (–0.13 to 1.14)
Reference group	57	6	0.55 (0.19 to 0.91)	28	5	0.40 (0.06 to 0.73)
<b>Duration of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
<b>Below the median: &lt; 64.9 (n = 319)</b>			<b>Above the median: ≥ 64.9 (n = 163)</b>			
≤ 2 weeks	2	48	5.75 (–5.85 to 17.35)	1	2	–4.50 (–19.47 to 10.46)
3 weeks	3	87	17.05 (9.33 to 24.76)	3	71	4.50 (–0.80 to 9.81)
4–10 weeks	4	46	15.00 (6.91 to 23.09)	3	32	4.20 (–1.46 to 9.86)
> 10–20 weeks	3	28	21.64 (11.30 to 31.97)	3	17	9.28 (3.06 to 15.51)
> 20 weeks	2	18	23.53 (12.09 to 34.96)	2	16	10.01 (2.42 to 17.60)
Reference group	2	47	14.91 (5.65 to 24.17)	2	18	13.65 (3.37 to 23.94)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
<b>Below the median: &lt; 35 (n = 395)</b>			<b>Above the median: ≥ 35 (n = 145)</b>			
≤ 2 weeks	6	70	4.02 (–0.64 to 8.69)	4	23	3.66 (–0.63 to 7.95)
3 weeks	2	68	5.89 (–0.08 to 11.86)	2	37	3.01 (–7.08 to 13.09)
4–10 weeks	3	55	3.66 (–2.08 to 9.40)	1	13	2.57 (–7.60 to 12.75)
> 10–20 weeks	5	65	4.85 (0.20 to 9.51)	5	28	2.73 (–1.52 to 6.97)
> 20 weeks	3	105	10.61 (3.91 to 17.30)	3	31	3.94 (–3.19 to 11.06)
Reference group	5	32	3.27 (–1.63 to 8.16)	4	13	2.22 (–1.98 to 6.43)
<i>Naming on the BNT, range 0–60</i>						
<b>Below the median: &lt; 23 (n = 304)</b>			<b>Above the median: ≥ 23 (n = 81)</b>			
≤ 4 weeks	5	63	4.59 (–2.87 to 12.05)	3	23	4.35 (–2.34 to 11.04)
> 4–10 weeks	3	22	8.22 (–0.44 to 16.88)	2	5	1.32 (–7.67 to 10.30)
> 10–20 weeks	4	71	7.52 (1.08 to 13.97)	3	15	8.87 (2.92 to 14.82)
> 20 weeks	3	108	7.79 (–0.11 to 15.69)	2	26	16.01 (6.60 to 25.41)
Reference group	5	40	7.80 (1.32 to 14.29)	4	12	5.60 (–0.80 to 12.00)
<i>Functional communication on the AAT-SSC,<sup>a</sup> range 0–5</i>						
<b>Below the median (moderate–severe): &lt; 2 (n = 243)</b>			<b>Above the median (mild–moderate): ≥ 2 (n = 231)</b>			
≤ 3 weeks	35	3	0.42 (–0.003 to 0.85)	20	2	0.71 (–0.03 to 1.44)
3 weeks	32	2	0.56 (0.09 to 1.03)	24	2	0.54 (0.01 to 1.07)
4–10 weeks	12	2	0.74 (0.04 to 1.44)	45	2	0.63 (0.08 to 1.19)

continued

TABLE 40 Severe vs. mild aphasia RCT participant subgroups; multivariable estimates of means (95% CIs) (continued)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
> 10–20 weeks	47	4	0.92 (0.56 to 1.28)	29	4	0.50 (0.06 to 0.95)
> 20 weeks	61	4	1.14 (0.78 to 1.49)	90	4	0.44 (-0.04 to 0.91)
Reference group	56	5	0.46 (0.12 to 0.79)	23	4	0.44 (-0.02 to 0.90)
<b>Intensity of SLT</b>						
Overall language ability on the WAB-AQ, range 0–100						
<b>Below the median: &lt; 64.9 (n = 319)</b>			<b>Above the median: ≥ 64.9 (n = 163)</b>			
≤ 2 hours weekly	3	55	18.40 (6.72 to 30.09)	3	19	7.13 (1.94 to 12.31)
> 2–3 hours weekly	7	70	13.13 (5.07 to 21.19)	6	23	4.32 (-0.48 to 9.12)
> 3–4 hours weekly	4	64	20.04 (10.14 to 29.94)	4	40	6.30 (1.54 to 11.07)
> 4–9 hours weekly	2	35	13.85 (2.80 to 24.89)	1	15	6.31 (0.68 to 11.94)
> 9 hours weekly	3	48	19.59 (10.41 to 28.78)	3	48	7.97 (3.37 to 12.57)
Reference group	2	47	16.40 (5.44 to 27.36)	2	18	8.91 (3.46 to 14.36)
Auditory comprehension on the TT-AAT, range 0–50						
<b>Below median: &lt; 35 (n = 395)</b>			<b>Above the median: ≥ 35 (n = 145)</b>			
≤ 2 hours weekly	2	9	9.07 (2.57 to 15.58)	2	10	1.13 (-4.61 to 6.87)
> 2–3 hours weekly	7	87	4.26 (0.02 to 8.50)	6	33	-3.23 (-8.25 to 1.78)
> 3–4 hours weekly	3	80	5.80 (-0.29 to 11.88)	3	32	3.28 (-3.19 to 9.74)
> 4–9 hours weekly	5	90	3.94 (-0.09 to 7.98)	3	13	-2.22 (-7.76 to 3.31)
> 9 hours weekly	6	97	8.90 (4.98 to 12.81)	6	44	1.45 (-3.24 to 6.15)
Reference group	5	32	3.59 (-1.05 to 8.22)	4	13	0.71 (-4.90 to 6.31)
Naming on the BNT, range 0–60						
<b>Below the median: &lt; 23 (n = 304)</b>			<b>Above the median: ≥ 23 (n = 81)</b>			
≤ 2 hours weekly	2	16	12.45 (4.25 to 20.64)	1	2	-0.70 (-12.57 to 11.16)
> 2–3 hours weekly	5	84	6.61 (-0.30 to 13.52)	3	17	7.32 (1.89 to 12.75)
> 3–4 hours weekly	3	96	9.60 (1.64 to 17.57)	2	31	8.21 (3.01 to 13.40)
> 4–9 hours weekly	2	41	6.40 (-2.02 to 14.83)	-	-	-
> 9 hours weekly	4	27	1.43 (-5.72 to 8.58)	4	19	9.45 (4.64 to 14.26)
Reference group	5	40	8.17 (1.73 to 14.62)	4	12	7.63 (2.01 to 13.24)
Functional communication on the AAT-SSC, <sup>a</sup> range 0–5						
<b>Below the median (moderate-severe): &lt; 2 (n = 280)</b>			<b>Above the median (mild-moderate): ≥ 2 (n = 253)</b>			
≤ 2 hours weekly	42	3	0.98 (0.34 to 1.62)	41	4	0.61 (0.24 to 0.98)
> 2–3 hours weekly	20	4	0.98 (0.40 to 1.55)	54	5	0.52 (0.11 to 0.93)
> 3–4 hours weekly	98	5	0.85 (0.45 to 1.25)	80	5	0.49 (0.14 to 0.84)
> 4–9 hours weekly	31	2	0.30 (-0.24 to 0.85)	28	2	0.59 (0.20 to 0.99)
> 9 hours weekly	33	6	0.85 (0.35 to 1.35)	27	4	0.63 (0.26 to 1.01)
Reference group	56	5	0.46 (0.06 to 0.86)	23	4	0.45 (0.06 to 0.84)

TABLE 40 Severe vs. mild aphasia RCT participant subgroups; multivariable estimates of means (95% CIs) (continued)

	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<b>Dosage of SLT</b>						
Overall language ability on the WAB-AQ, range 0–100						
<b>Below the median: &lt; 64.9 (n = 319)</b>			<b>Above the median: ≥ 64.9 (n = 163)</b>			
≤ 5 hours	6	79	10.88 (3.58 to 18.17)	5	22	3.86 (-1.26 to 8.98)
> 5–14 hours	4	72	18.17 (10.62 to 25.73)	4	42	5.97 (1.01 to 10.93)
> 14–20 hours	4	48	19.17 (11.47 to 26.88)	4	41	5.10 (0.22 to 9.99)
> 20–< 50 hours	3	23	23.49 (13.50 to 33.48)	2	8	8.73 (1.95 to 15.51)
≥ 50 hours	4	42	17.92 (9.24 to 26.61)	3	26	8.39 (2.55 to 14.24)
Reference group	4	53	11.66 (3.06 to 20.26)	4	24	7.00 (1.81 to 12.19)
Auditory comprehension on the TT-AAT, range 0–50						
<b>Below the median: &lt; 35 (n = 395)</b>			<b>Above the median: ≥ 35 (n = 145)</b>			
≤ 5 hours	3	54	0.94 (-3.83 to 5.71)	1	10	-0.04 (-7.25 to 7.17)
> 5–14 hours	3	61	2.65 (-1.87 to 7.16)	2	25	-1.77 (-8.43 to 4.89)
> 14–20 hours	2	45	5.44 (0.56 to 10.32)	2	21	0.84 (-5.88 to 7.55)
> 20–< 50 hours	5	58	5.47 (1.03 to 9.92)	7	32	0.75 (-4.50 to 5.99)
≥ 50 hours	6	142	8.89 (4.49 to 13.30)	5	41	-1.51 (-7.12 to 4.09)
Reference group	6	35	3.81 (-0.78 to 8.39)	5	16	0.84 (-4.69 to 6.36)
Naming on the BNT, range 0–60						
<b>Below the median: &lt; 23 (n = 304)</b>			<b>Above the median: ≥ 23 (n = 81)</b>			
≤ 5 hours	2	28	14.44 (2.05 to 26.84)	-	-	-
> 5–20 hours	4	46	6.66 (-2.87 to 16.18)	2	15	2.86 (-1.68 to 7.41)
> 20–50 hours	5	62	8.90 (0.11 to 17.69)	4	19	9.44 (5.57 to 13.31)
> 50–100 hours	2	98	8.82 (-7.65 to 25.29)	1	24	7.24 (2.27 to 12.20)
> 100 hours	3	30	-4.80 (-14.98 to 5.38)	3	11	12.96 (8.51 to 17.41)
Reference group	5	40	8.11 (-0.59 to 16.81)	4	12	8.21 (3.33 to 13.09)
Functional communication on the AAT-SSC, <sup>a</sup> range 0–5						
<b>Below the median (moderate–severe): &lt; 2 (n = 275)</b>			<b>Above the median (mild–moderate): ≥ 2 (n = 248)</b>			
≤ 5 hours	19	3	-0.10 (-0.62 to 0.42)	28	3	0.54 (0.13 to 0.96)
> 5–14 hours	48	5	0.64 (0.29 to 1.99)	56	5	0.49 (0.12 to 0.85)
> 14–20 hours	3	1	0.84 (-0.36 to 2.04)	8	3	0.69 (0.15 to 1.22)
> 20–50 hours	71	7	0.82 (0.53 to 1.15)	25	7	0.55 (0.17 to 0.92)
≥ 50 hours	72	6	1.07 (0.78 to 1.37)	102	7	0.57 (0.23 to 0.92)
Reference group	62	7	0.41 (0.12 to 0.71)	29	6	0.40 (0.04 to 0.77)
-, Insufficient data.						
a Observer rated, including TOMs activity data.						
Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.						

TABLE 41 Female vs. male RCT participant subgroups; multivariable estimates of means (95% CIs)

	Female (IPD 211)			Male (IPD 329)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<b>Base model</b>						
<i>Overall language ability on the WAB-AQ, range 0-100</i>						
55 years	10	55	16.28 (8.84 to 23.72)	11	81	14.08 (7.70 to 20.46)
56-65 years	10	42	13.68 (6.01 to 21.36)	11	99	10.92 (4.70 to 17.14)
66-75 years	9	41	15.07 (7.15 to 22.99)	10	55	8.86 (2.03 to 15.68)
> 75 years	6	68	16.63 (8.38 to 24.89)	7	41	12.17 (4.75 to 19.59)
0-1 month	7	127	22.86 (16.17 to 29.55)	8	133	16.07 (9.99 to 22.16)
> 1-3 months	5	23	18.46 (9.78 to 27.13)	6	41	14.58 (7.56 to 21.59)
> 3-6 months	3	7	11.15 (-3.24 to 25.54)	3	9	8.29 (-3.37 to 19.95)
> 6 months	3	49	9.20 (-3.52 to 21.93)	4	93	7.09 (-2.10 to 16.27)
<i>Auditory comprehension on the TT-AAT, range 0-50</i>						
≤ 55 years	13	75	6.27 (2.95 to 9.59)	15	103	6.05 (2.72 to 9.39)
56-65 years	15	60	3.98 (0.58 to 7.38)	16	122	2.36 (-0.90 to 5.61)
66-75 years	13	42	5.87 (2.15 to 9.59)	15	74	2.47 (-1.00 to 5.94)
> 75 years	8	34	2.93 (-1.06 to 6.91)	10	30	1.13 (-3.16 to 5.42)
0-1 month	6	67	5.53 (1.55 to 9.51)	6	72	6.00 (1.58 to 10.41)
> 1-3 months	9	45	5.13 (1.36 to 8.90)	9	52	4.19 (0.30 to 8.09)
> 3-6 months	3	22	5.70 (-0.84 to 12.24)	6	39	1.43 (-4.12 to 6.97)
> 6 months	8	77	2.69 (-1.41 to 6.80)	8	166	0.39 (-3.34 to 4.12)
<i>Naming on the BNT, range 0-60</i>						
≤ 55 years	11	48	10.35 (4.35 to 16.34)	12	55	7.88 (3.32 to 12.44)
56-65 years	13	39	9.44 (3.33 to 15.54)	13	85	6.42 (2.13 to 10.71)
66-75 years	11	41	6.69 (0.46 to 12.91)	12	56	6.68 (2.10 to 11.25)
> 75 years	10	37	3.59 (-2.70 to 9.89)	8	24	7.72 (2.03 to 13.42)
0-1 month	5	63	8.54 (1.45 to 15.63)	5	66	15.93 (10.23 to 21.63)
> 1-3 months	8	41	8.86 (2.34 to 15.39)	7	52	7.62 (2.75 to 12.52)
> 3-6 months	4	26	7.46 (-0.85 to 15.76)	6	44	2.10 (-4.03 to 8.24)
> 6 months	6	35	5.21 (-2.15 to 12.57)	7	58	3.05 (-2.08 to 8.18)
<i>Functional communication on the AAT-SSC,<sup>a</sup> range 0-5 (female, n = 237; male, n = 296)</i>						
≤ 55 years	12	70	1.01 (0.56 to 1.46)	13	77	0.49 (0.25 to 0.72)
56-65 years	12	39	0.81 (0.33 to 1.30)	13	106	0.56 (0.35 to 0.76)
66-75 years	14	52	0.74 (0.27 to 1.21)	13	70	0.44 (0.20 to 0.67)
> 75 years	12	76	0.77 (0.31 to 1.23)	10	43	0.60 (0.30 to 0.91)
0-1 month	6	115	1.07 (0.54 to 1.60)	6	117	1.15 (0.93 to 1.38)
> 1-3 months	5	36	1.05 (0.51 to 1.59)	5	32	0.65 (0.31 to 0.99)
> 3-6 months	2	23	0.80 (0.01 to 1.59)	4	40	0.11 (-0.25 to 0.47)
> 6 months	7	63	0.41 (-0.10 to 0.93)	7	107	0.17 (-0.07 to 0.40)

TABLE 41 Female vs. male RCT participant subgroups; multivariable estimates of means (95% CIs) (continued)

	Female (IPD 211)			Male (IPD 329)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<b>Frequency of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
≤ 2 days per week	5	37	15.51 (6.22 to 24.80)	5	53	7.96 (0.25 to 15.67)
> 2–3 days per week	2	5	24.22 (7.73 to 40.71)	2	16	8.63 (–1.37 to 18.64)
> 3–4 days per week	5	24	14.27 (3.66 to 24.89)	4	50	11.38 (2.98 to 19.77)
> 4–5 days per week	5	90	16.44 (8.10 to 24.78)	6	104	13.20 (6.13 to 20.27)
> 5 days per week	2	11	15.95 (3.07 to 28.84)	2	21	13.59 (4.30 to 22.88)
Reference group	3	39	12.12 (1.84 to 22.41)	3	32	15.00 (6.14 to 23.87)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
≤ 2 days per week	4	25	3.25 (–1.49 to 7.98)	4	39	–2.32 (–6.61 to 1.97)
> 2–3 days per week	4	30	4.42 (–1.09 to 9.92)	4	59	0.87 (–3.61 to 5.35)
> 3–4 days per week	5	52	8.13 (2.65 to 13.60)	4	62	4.93 (0.03 to 9.84)
> 4–5 days per week	8	72	4.32 (0.52 to 8.12)	8	99	5.06 (1.41 to 8.71)
> 5 days per week	3	14	2.65 (–2.99 to 8.30)	3	37	2.82 (–1.96 to 7.60)
Reference group	6	18	3.25 (–1.72 to 8.30)	6	33	1.89 (–2.54 to 6.32)
<i>Naming on the BNT, range 0–60</i>						
≤ 2 days per week	4	17	17.05 (9.47 to 24.64)	4	25	10.58 (4.29 to 16.86)
> 2–3 days per week	3	28	6.99 (–2.22 to 16.19)	3	56	5.93 (–0.70 to 12.55)
> 3–4 days per week	4	48	8.83 (0.24 to 17.43)	3	54	8.56 (1.45 to 15.67)
> 4–5 days per week	6	50	3.47 (–3.18 to 10.12)	6	54	5.30 (0.01 to 10.58)
> 5 days per week	–	–	–	–	–	–
No SLT/O	5	21	7.35 (0.36 to 14.33)	5	31	8.01 (2.53 to 13.49)
<i>Functional communication observer rated on the AAT-SSC,<sup>a</sup> range 0–5 (female, n = 237; male, n = 296)</i>						
≤ 2 times a week	4	32	0.80 (0.23 to 1.38)	5	50	0.38 (0.06 to 0.69)
> 2–3 days per week	3	32	0.95 (0.27 to 1.64)	3	61	0.47 (0.14 to 0.81)
> 3–4 days per week	3	49	1.01 (0.21 to 1.81)	3	53	0.58 (0.21 to 0.94)
> 4–5 days per week	9	78	0.80 (0.31 to 1.29)	9	77	0.68 (0.42 to 0.95)
> 5 days per week	1	3	0.27 (–1.03 to 1.58)	3	6	0.81 (0.09 to 1.53)
Reference group	6	41	0.69 (0.16 to 1.22)	6	44	0.25 (–0.05 to 0.56)
<b>Duration of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
≤ 2 weeks	2	25	5.80 (–5.07 to 16.66)	2	25	1.78 (–9.87 to 13.44)
3 weeks	3	65	12.19 (5.05 to 19.33)	3	93	11.62 (4.75 to 18.49)
4–10 weeks	3	23	15.19 (6.54 to 23.85)	4	55	9.43 (2.32 to 16.53)
> 10–20 weeks	3	19	19.73 (9.16 to 30.27)	3	26	16.72 (7.79 to 25.65)
> 20 weeks	2	12	24.52 (13.22 to 35.81)	2	22	13.20 (3.33 to 23.08)
Reference group	2	36	8.09 (–0.87 to 17.06)	2	29	16.58 (8.16 to 25.00)

continued

TABLE 41 Female vs. male RCT participant subgroups; multivariable estimates of means (95% CIs) (continued)

	Female (IPD 211)			Male (IPD 329)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
≤ 2 weeks	5	38	4.36 (–0.71 to 9.43)	6	55	5.28 (–1.23 to 11.79)
3 weeks	2	42	4.31 (–2.21 to 10.82)	2	63	3.37 (–5.33 to 12.06)
4–10 weeks	3	18	3.13 (–3.46 to 9.73)	3	50	1.47 (–6.98 to 9.92)
> 10–20 weeks	5	35	4.36 (–0.58 to 9.29)	5	58	9.25 (2.91 to 15.59)
> 20 weeks	3	63	6.97 (0.83 to 13.11)	3	73	–10.75 (–19.03 to –2.48)
Reference group	5	15	3.55 (–2.14 to 9.23)	5	30	6.17 (–0.27 to 12.61)
<i>Naming on the BNT, range 0–60</i>						
≤ 4 weeks	5	38	5.18 (–3.82 to 14.19)	5	48	4.74 (–1.22 to 10.69)
4–10 weeks	3	9	4.21 (–6.64 to 15.07)	3	18	7.66 (–0.25 to 15.58)
> 10–20 weeks	3	35	4.11 (–4.39 to 12.60)	4	51	11.03 (5.38 to 16.67)
> 20 weeks	3	62	20.29 (9.39 to 31.18)	3	72	4.99 (–1.83 to 11.74)
Reference group	5	21	2.78 (–5.62 to 11.18)	5	31	10.12 (4.26 to 15.98)
<i>Functional communication observer rated on the AAT-SSC,<sup>a</sup> range 0–5 (female, n = 237; male, n = 296)</i>						
≤ 3 weeks	4	30	0.45 (–0.31 to 1.20)	3	25	0.22 (–0.14 to 0.59)
3 weeks	2	24	0.54 (–0.20 to 1.28)	2	32	0.59 (0.24 to 0.93)
4–10 weeks	2	16	0.97 (0.09 to 1.84)	2	41	0.58 (0.20 to 0.96)
> 10–20 weeks	4	30	0.90 (0.25 to 1.54)	4	46	0.67 (0.40 to 0.95)
> 20 weeks	4	71	0.90 (0.25 to 1.54)	4	80	0.62 (0.38 to 0.85)
Reference group	5	38	0.58 (–0.04 to 1.21)	5	41	0.20 (–0.10 to 0.49)
<b>Intensity of SLT</b>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
≤ 2 hours weekly	3	37	18.53 (7.46 to 29.59)	3	37	13.28 (4.07 to 22.50)
> 2–3 hours weekly	7	37	16.54 (7.34 to 25.74)	7	56	6.56 (–0.13 to 13.25)
> 3–4 hours weekly	4	41	14.68 (4.33 to 25.03)	4	63	14.73 (7.21 to 22.24)
> 4–9 hours weekly	2	20	13.14 (1.42 to 24.85)	2	30	10.72 (2.17 to 19.26)
> 9 hours weekly	3	35	15.60 (5.95 to 25.25)	3	61	15.13 (7.92 to 22.34)
Reference group	2	36	10.19 (–1.50 to 21.89)	2	29	17.69 (8.82 to 26.57)
<i>Auditory Comprehension on the TT-AAT, range 0–50</i>						
≤ 2 hours weekly	2	10	7.91 (1.82 to 14.00)	2	9	5.94 (–0.68 to 12.55)
> 2–3 hours weekly	7	42	3.29 (–1.00 to 7.57)	7	79	–0.73 (–4.74 to 3.29)
> 3–4 hours weekly	3	57	6.35 (0.27 to 12.42)	3	55	6.61 (0.76 to 12.46)
> 4–9 hours weekly	5	37	3.55 (–0.93 to 8.03)	5	66	2.22 (–1.91 to 6.34)
> 9 hours weekly	6	50	6.97 (2.89 to 11.04)	6	91	7.63 (3.77 to 11.48)
Reference group	5	15	3.91 (–1.54 to 9.35)	5	30	1.12 (–3.53 to 5.77)

TABLE 41 Female vs. male RCT participant subgroups; multivariable estimates of means (95% CIs) (continued)

	Female (IPD 211)			Male (IPD 329)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<i>Naming on the BNT, range 0–60</i>						
≤ 2 hours weekly	2	8	12.19 (1.72 to 22.65)	2	10	15.54 (6.94 to 24.14)
> 2–3 hours weekly	5	38	13.48 (4.67 to 22.30)	5	63	4.53 (–1.41 to 10.47)
> 3–4 hours weekly	3	59	7.24 (–3.10 to 17.57)	3	68	8.87 (2.10 to 15.63)
> 4–9 hours weekly	2	20	4.74 (–6.96 to 16.40)	2	21	5.18 (–3.11 to 13.46)
> 9 hours weekly	4	19	1.34 (–7.34 to 10.02)	4	27	6.54 (0.13 to 12.95)
Reference group	5	21	5.01 (–3.31 to 13.32)	5	31	8.91 (3.13 to 14.68)
<i>Functional communication on the AAT-SSC,<sup>a</sup> range 0–5 (female, n = 237; male, n = 296)</i>						
≤ 2 hours weekly	4	39	1.15 (0.47 to 1.87)	4	44	0.48 (0.14 to 0.83)
> 2–3 hours weekly	5	30	1.03 (0.34 to 1.73)	5	44	0.58 (0.23 to 0.92)
> 3–4 hours weekly	5	81	0.75 (0.16 to 1.34)	5	97	0.65 (0.40 to 0.89)
> 4–9 hours weekly	2	25	0.65 (–0.03 to 1.32)	2	34	0.37 (–0.01 to 0.74)
> 9 hours weekly	6	24	0.74 (0.12 to 1.37)	6	36	0.60 (0.26 to 0.93)
Reference group	5	38	0.63 (0.06 to 1.20)	5	41	0.22 (–0.09 to 0.53)
<i>Dosage of SLT</i>						
<i>Overall language ability on the WAB-AQ, range 0–100</i>						
≤ 5 hours	6	48	12.70 (4.67 to 20.74)	6	53	6.63 (–0.39 to 13.66)
> 5–> 14 hours	4	44	17.52 (9.07 to 25.97)	4	70	11.63 (4.86 to 18.40)
14.1–20 hours	4	32	18.07 (9.50 to 26.63)	4	57	11.44 (4.55 to 18.33)
> 20.1–< 50 hours	2	13	24.37 (12.22 to 36.52)	4	18	15.61 (6.23 to 25.00)
≥ 50 hours	4	28	14.21 (4.78 to 23.64)	4	40	15.25 (6.97 to 23.53)
Reference group	4	40	11.98 (2.44 to 21.52)	4	37	11.60 (3.80 to 19.39)
<i>Auditory comprehension on the TT-AAT, range 0–50</i>						
≤ 5 hours	3	24	2.36 (–2.86 to 7.58)	3	40	–1.07 (–6.32 to 4.18)
> 5–> 14 hours	4	34	2.80 (–2.02 to 7.62)	4	52	0.23 (–4.70 to 5.17)
> 14–20 hours	2	24	5.07 (–0.16 to 10.31)	2	42	2.95 (–2.38 to 8.27)
> 20–< 50 hours	6	34	4.45 (0.08 to 8.83)	7	56	6.48 (1.78 to 11.17)
≥ 50 hours	6	77	7.02 (2.88 to 11.15)	6	106	3.28 (–1.44 to 8.01)
Reference group	6	18	2.70 (–2.23 to 7.64)	6	33	3.75 (–1.09 to 8.59)
<i>Naming on the BNT, range 0–60</i>						
≤ 5 hours	2	10	6.25 (–10.42 to 22.93)	2	18	7.55 (–2.64 to 17.73)
> 5–20 hours	4	28	6.15 (–3.95 to 16.25)	4	33	3.51 (–4.05 to 11.08)
> 20–< 50 hours	5	32	10.91 (1.96 to 19.87)	5	49	11.76 (5.07 to 18.45)
50–< 100 hours	2	58	7.60 (–8.13 to 23.33)	2	64	7.31 (–3.08 to 17.70)
≥ 100 hours	3	16	5.19 (–5.55 to 15.93)	3	25	2.60 (–5.66 to 10.86)
Reference group	5	21	7.80 (–1.27 to 16.87)	5	31	10.50 (3.69 to 17.30)

continued

TABLE 41 Female vs. male RCT participant subgroups; multivariable estimates of means (95% CIs) (continued)

	Female (IPD 211)			Male (IPD 329)		
	RCTs (n)	IPD (n)	Estimate of mean (95% CI)	RCTs (n)	IPD (n)	Estimate of mean (95% CI)
<i>Functional communication on the AAT-SSC,<sup>a</sup> range 0–5 (female, n = 237; male, n = 296)</i>						
≤ 5 hours	3	21	0.46 (–0.20 to 1.13)	3	26	0.27 (–0.12 to 0.66)
> 5–14 hours	5	42	0.92 (0.35 to 1.49)	5	62	0.42 (0.17 to 0.67)
> 14–20 hours	2	4	1.59 (0.57 to 2.61)	2	7	0.46 (–0.20 to 1.12)
> 20–< 50 hours	8	43	0.90 (0.38 to 1.42)	8	53	0.60 (0.32 to 0.88)
≥ 50 hours	7	82	0.81 (0.26 to 1.36)	6	93	0.70 (0.48 to 0.91)
Reference group	7	42	0.67 (0.13 to 1.21)	7	49	0.16 (–0.11 to 0.43)
–, Insufficient data.						
a Including TOMs activity data.						
Shading indicates evidence of positive (statistically significant) change from baseline. Unshaded data provide no evidence of a change from baseline in the group/on that measure.						



EME  
HSDR  
HTA  
PGfAR  
PHR

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