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44

45 **Consortium Name:**

46 **Therapeutics for Dementia Consortium**

47 **Abstract**

48 Since the G8 Dementia Summit in 2013, a number of initiatives have been established with the aim
49 of facilitating the discovery of a disease-modifying treatment for dementia by 2025. This report is a
50 summary of the findings and recommendations of a meeting titled ‘Tackling gaps in developing life-
51 changing treatments for dementia’, hosted by Alzheimer’s Research UK in May 2018. The aim of the
52 meeting was to identify, review and highlight the areas in dementia research that are not currently
53 being addressed by existing initiatives. It reflects the views of leading experts in the field of
54 neurodegeneration research challenged with developing a strategic action plan to address these
55 gaps and make recommendations on how to achieve the G8 Dementia Summit goals. The plan calls
56 for significant advances in: (1) translating newly identified genetic risk factors into a better
57 understanding of the impacted biological processes; (2) enhanced understanding of selective
58 neuronal resilience to inform novel drug targets; (3) facilitating robust and reproducible drug target
59 validation; (4) appropriate and evidence-based selection of appropriate subjects for proof-of-
60 concept clinical trials; (5) improving approaches to assess drug-target engagement in humans; and
61 (6) innovative approaches to conducting clinical trials if we are able to detect disease 10-15 years
62 earlier than we currently do today.

63 Keywords: Alzheimer’s disease; Dementia; Disease-modifying treatment; Earlier detection;
64 Diagnosis; Neurodegeneration; Target validation; Clinical trials; Genetic risk factors

65 **1. Introduction**

66 Alzheimer’s disease (AD), and other diseases that cause dementia, are the greatest health and social
67 care challenges of our age [1]. Today, there are 50 million people living with dementia worldwide
68 and this is projected to increase to 135 million by 2050 due to a rise in life expectancy and an ageing
69 population [2, 3]. Current therapeutics for AD can transiently improve cognitive symptoms in some
70 patients, but they do not treat the underlying causes of dementia or slow the rate of disease
71 progression [3, 4]. Since the success rate for the development of disease-modifying drugs for

72 dementia diseases has been disappointing, such as the failure of beta-secretase 1 inhibitors to show
73 efficacy, it is important to reconsider what the real barriers to progress in this field are and identify
74 emerging opportunities. It is intended that this analysis should inform the development of a
75 strategic action plan that will contribute to the G8 ambition of delivering a disease-modifying
76 treatment for dementia by 2025, and support progress towards and beyond this goal [3].

77 **2. Background**

78 In December 2013 the UK government hosted the G8 Dementia Summit to enable the members of
79 the constituent countries to discuss and formulate an international approach to the global challenge
80 of dementia [5]. The G8 stated that dementia research should be made a global priority with a key
81 aim of developing a cure or disease-modifying therapy by 2025 [3, 5]. During the Summit, it was also
82 agreed that dementia research was under resourced and funded [5]; this has subsequently led to the
83 establishment of a number of important research initiatives aimed at addressing this specific
84 challenge [6-10]. For example in the UK, in 2015, the UK Government published the 'Challenge on
85 Dementia 2020', an iteration of the 2012 Dementia Challenge, outlining the government's aims to
86 improve dementia care, support and research by 2020 [6]. To meet this challenge in the UK the
87 Medical Research Council (MRC), part of UK Research and Innovation, founded the Dementias
88 Platform UK (DPUK) [7] in 2014 with £50 million support for coordinated data and clinical research
89 infrastructures and experimental medicine collaborations with industry. The Dementia Discovery
90 Fund [8] was established in 2015 as a global venture capital fund with the aim of investing in new
91 and emerging disease-modifying therapeutic approaches and facilitating the progression of potential
92 new drug targets through to early clinical development and testing. Also in 2015, the Drug Discovery
93 Alliance (DDA) [9] was launched by Alzheimer's Research UK (ARUK), bringing together three
94 institutes (University of Cambridge, University of Oxford and University College London) with the aim
95 of bridging the gap between discovery science and drug development. In addition, the UK Dementia
96 Research Institute (UK DRI) [10] was founded in 2016, comprising six centres within universities
97 across the UK, with £290 million of co-funding from the MRC, ARUK and the Alzheimer's Society.

98 Together, the DDA, DPUK and UK DRI aim to transform the treatment, care, prevention and
99 diagnosis of dementia, through coordinated discovery science and translation to people living with
100 dementia.

101 Despite these and other efforts, significant gaps still exist that hamper the development of disease-
102 modifying treatments for dementias. To address these gaps, ARUK convened a panel of experts in
103 the dementia field, including global academic and industry researchers, to identify and prioritise key
104 thematic areas that are not the current focus of research and funding initiatives in this field. During
105 15 and 16 May 2018 the panel met in London, UK to discuss how to tackle each specific gap and
106 develop an action plan around each theme. The action plan was intended to be future looking, to
107 provide important information to facilitate the progress of dementia research and ultimately inform
108 and direct the development of life-changing treatments for dementia.

109 The meeting was organised around six themes: (1) translating genetic risk factors into biological
110 processes; (2) better understanding neuronal resilience to inform novel drug targets; (3) facilitating
111 robust and reproducible drug target validation; (4) identifying appropriate populations of
112 appropriate subjects for Phase IIa proof-of-concept clinical trials; (5) improving approaches to assess
113 drug-target engagement in humans; and (6) innovative approaches to conducting clinical trials if we
114 are able to detect dementia diseases 10-15 years earlier than we are able to today. Each theme will
115 be reviewed in this paper and the key recommendations are outlined. We also include a preliminary
116 action plan to attempt to begin to address and resolve these recommendations.

117 **3. Translating genetic risk factors into biological processes**

118 Understanding genetic vulnerability and its impact on neuronal health and biology
119 Important advances have been made in identifying genetic factors that contribute to the risk of
120 developing diseases that may cause dementia, and particularly AD. Mutations in amyloid precursor
121 protein and presenilin 1 and 2 cause autosomal dominant AD, and the apolipoprotein E (*APO E*) $\epsilon 4$
122 allele is a major risk-factor for late onset AD [11]. A key goal of current AD research is to seek out

123 novel disease-risk genes, elucidate their biological function in the development of the disease and
124 try to interpret important gene-gene or gene-environment interactions with the aim of identifying
125 novel approaches to the treatment and prevention of AD and other neurodegenerative diseases. The
126 standard method for identifying disease-risk genes has been genome-wide association studies
127 (GWAS), and this approach has led to the identification of (at least) an additional 21 genetic risk loci
128 [12]. However, these are highly complex diseases likely caused by the composite action of multiple
129 disease-related genes. This compounds the challenge of translating genetic findings into functional
130 mechanisms that are important in disease pathogenesis [12] and consequently, valid targets for the
131 development of effective therapeutics. Discussions in this session focussed on approaches to
132 improve the translation of genetic findings into disease biology using a more integrated biology
133 approach, better tools and analysis of genotype-phenotype correlations to provide a more
134 comprehensive understanding of disease causation and inform future therapeutic drug discovery
135 and biomarkers.

136 As many genetic factors having been identified as contributing to the risk for developing AD, the
137 research focus has shifted from identifying novel risk factors toward understanding how such risk
138 factors lead to changes in biological processes and pathways, some of which are already known to
139 be affected in dementing and other neurodegenerative diseases. Moving from genetic data to a
140 potential therapeutic will involve different tools and areas of expertise, including *in silico* and
141 laboratory approaches to structural biology, cell biology, and pharmacology. Leveraging emerging
142 technologies (such as single cell studies or induced pluripotent stem cell models) will also enable
143 acceleration of the investigation of the links between genetic data and potential therapeutics. The
144 Open Targets partnership is a good example of this approach [13]. It brings together expertise from
145 six different institutions and uses human genetics and genomics data to systematically identify and
146 prioritise drug targets for therapeutic development [13]. Another good example is seen in
147 schizophrenia research, where understanding the role of the complement component 4 locus
148 involved the application of different tools and datasets (including GWAS and expression data from

149 post-mortem brains), and genetic engineering of animal models to understand the biological
150 mechanism [14]. This approach identified potential biological targets from genetic data that may
151 result in the development of novel therapeutics. These examples of partnerships and collaborations,
152 and application of different tools, should be more widely adopted by the dementia research
153 community to bridge the gap between genetic signals to biologically relevant therapeutic targets.
154 Interdisciplinarity and development/application of a broad range of tools and technologies are also
155 at the heart of the UK DRI research network, aiming to accelerate our mechanistic understanding of
156 dementia to find new ways to prevent, diagnose and treat dementia effectively [10].

157 A significant challenge in translating genetic data into biological processes is the lack of
158 understanding of the underlying role of individual genes, and how they relate to disease progression
159 and phenotype in later life. Genomic analysis across the natural history of the disease would enable
160 a better understanding of the genes involved at different stages of disease, provide additional
161 insight into the disease mechanism(s) and inform the development of alternative interventions or
162 new areas of research. Part of this genetic analysis should also include identification of the genetic
163 influences on rate of disease progression. This could be approached by capitalising on longitudinally
164 phenotyped cohorts that include and contrast subjects with sporadic AD to analyse the genotype-
165 phenotype interactions and progression of the disease.

166 To support these approaches, it will be important to identify key expertise from different disciplines
167 that are currently missing from dementia research and proactively engage with subject matter
168 experts from diverse areas such as data science, not only to bring that expertise into the dementia
169 field but also to promote the exchange of knowledge and innovation. Barriers to collaborative and
170 interdisciplinary research also need to be understood and addressed. For example, intra-institutional
171 collaborations may have been hindered in the UK by the fact that a publication could only be
172 submitted once to the former Research Excellence Framework assessments from each institution
173 [15]. The evaluation of collaborative research outputs has changed, with a greater emphasis on

174 impact and contribution, but further changes in the evaluation and recognition process are needed if
175 we are to foster true collaborative efforts.

176 There is also a need to bring together experts from other relevant disease and basic science areas of
177 expertise, particularly those shown to have an increasingly important role in dementia research (e.g.
178 immunologists and lipid biologists), and to encourage intra- and interdisciplinary collaboration. This
179 approach has been successful in Huntington's disease research, where the CHDI Foundation
180 (<https://chdifoundation.org/>) manages a network of over 600 researchers worldwide, facilitating the
181 sharing of ideas and information that encourages active collaboration. A similar model could be
182 adopted for dementia research. Dementia symposia and workshop sessions could be included in
183 conferences hosted by other disciplines, such as immunology and oncology. Similarly, subject matter
184 experts in relevant fields could chair these symposia or workshops (e.g. asking immunologists to lead
185 neuroinflammation discussions). Such approaches would encourage cross-discipline fertilisation and
186 potentially bring new expertise into the dementia field.

187 This approach has been adopted by the DPUK for experimental medicine working groups, and the
188 Wellcome Trust Consortium for the Neuroimmunology of Mood Disorders and Alzheimer's Disease
189 (NIMA) [16]. The NIMA Consortium is investigating novel therapeutic and biomarker approaches for
190 neurodegeneration based on the biological links between inflammation and neurodegeneration and
191 a number of clinical compounds derived from immunology drug discovery. To address this challenge,
192 the Consortium assembled a team of academic and industry scientists with diverse expertise in
193 imaging, animal models, clinical phenotyping and informatics. Such collaborative and
194 interdisciplinary approaches could facilitate the translation of genetic research that impacts on cell
195 biology into neurodegenerative research and development.

196

197

198 **Summary of recommendations and suggested actions**

199 **3.1.1.** Facilitate translation of genetic risk factors into targetable biological processes and
200 pathways using a more integrated biology approach

201 **3.1.2.** Support the application of tools and expertise from other fields to better translate
202 genetic information into cell biology and drug development

203 **3.1.3.** Encourage research that seeks to carry out genomic analysis along disease
204 progression to identify the genes involved at different stages of disease

205 **3.1.4.** Support interdisciplinary collaboration, and the development of dementia symposia
206 and workshop sessions in other relevant disciplines to foster cross-fertilisation of ideas
207 and bring new expertise into the dementia field.

208

209 **4. Better understanding selective neuronal vulnerability and resilience to inform**
210 **novel drug targets**

211 Could a better understanding of why some neurones die and others are resistant to cell
212 death identify novel drug targets?

213 This session was focused on why some neuronal cell populations die very early in the course of the
214 disease, others die at a later stage and still others do not seem to degenerate at all, and whether
215 understanding this difference could help identifying novel targets for drug development. Recent
216 research has identified multiple neurodegenerative pathways that result in a domino-like cascade of
217 events that eventually lead to the development of dementias. However, these changes are not seen
218 in all cases of AD [17, 18]. The characteristic features of AD are the pathological accumulation of
219 extracellular plaques composed of amyloid- β protein and intraneuronal tangles consisting of altered
220 forms of tau [17]. A long-standing puzzle in AD research has been the finding that there may be a
221 substantial number of A β plaques in the brain of some individuals who have otherwise normal
222 cognition and conversely people who exhibit phenotypic AD but have little or no plaque or tangle

223 deposition [19, 20] Studies show that A β deposition is an early event that may play a harmful role in
224 the development of AD, however, the mechanisms that link A β to neurodegeneration are poorly
225 understood. Moreover, intermediate A β species (e.g. oligomers) perhaps contribute more to nerve
226 injury than to plaques [21]. Clinically relevant symptoms tend to emerge around the same time that
227 tau pathology is correlated with cell death, although it is also acknowledged that the intermediate
228 oligomeric species may play a critical role in such developments [22]. Moreover, some brain regions
229 (hippocampus, amygdala and cerebral cortex) appear to show a selective vulnerability to plaque
230 accumulation and tau associated neurodegeneration, while others (basal ganglia, cerebellum, brain
231 stem and spinal cord) are initially spared [23, 24].

232 These observations suggest that understanding why some brain structures are more vulnerable to
233 insults than others could be gained by examining the molecular differences between neurones that
234 are susceptible to neurodegeneration and those that are relatively protected. For example,
235 excitatory but not inhibitory neurons, that differ in their expression of proteins that enable protein
236 degradation, accumulate damaging tau aggregates in a genetically engineered mouse model of tau
237 pathology spread [25]. This type of approach may aid the identification of novel disease mechanisms
238 that could be exploited to develop alternative therapeutic targets for disease management with a
239 potentially higher success rate for treatment. For example, recent studies have explored the locus
240 coeruleus, a brainstem nucleus in the central nervous system (CNS) that is the primary site for
241 production of noradrenaline and has diffuse noradrenergic innervation. Noradrenergic neurons in
242 this region play a central role in normal cognitive function, and so loss of innervation in this region is
243 postulated to be linked to cognitive decline, suggesting that noradrenaline signalling in the CNS
244 might be a viable therapeutic target [26].

245 The key advance enabling this approach was the possibility of biologically mapping the molecular
246 signature of different neuronal populations in healthy brains versus brains from subjects with
247 neurodegenerative diseases. This may lead to a better understanding of the biological processes

248 associated with neuronal vulnerability and may allow for a spatial and chronological characterisation
249 of the neural cell systems affected in dementia. The Allen Institute is making progress in this area,
250 with a project entitled Aging, Dementia and Traumatic Brain Injury Study [27] within the Allen Brain
251 Atlas [28]. It would be very useful to explore and expand the potential of these projects by
252 integrating data from different research groups globally. This requires overcoming barriers to data
253 sharing, data accessibility and integrative approaches across institutions to enable
254 interconnection/interoperability and linkage of datasets. A complementary approach to mapping
255 neuronal vulnerability has also been suggested at the National Institute of Health AD Summit 2018
256 [29] to develop an AD connectivity map based on 'omics' expression signatures in disease-relevant
257 cell types. Further investigation using an omics-based approach could systematically map resilience
258 and vulnerability by brain region as well as tracking the trajectory of the disease [30]. Integrating
259 multiple sets of omics data using computational and statistical tools can be used to analyse the
260 molecular pathways in specific brain regions and perhaps identify the more vulnerable pathways.
261 Others have suggested that additional approaches are needed, such as a more active investigation of
262 glia and vascular changes [31].

263 This could be studied using longitudinal structural magnetic resonance imaging (MRI) or synapse
264 positron-emission tomography (PET) imaging, however another important aspect is the evaluation of
265 post-mortem or resected human tissue, something that is not necessarily straightforward to obtain
266 from well characterised cases and without significant post-mortem delay, required for high-quality
267 samples. It was proposed that researchers need better access to living tissue from people living with
268 dementia, and the panel recommended that this be achieved by enabling access to resected tissue
269 from surgeries and utilising excess biopsy tissue. One approach suggested to streamline access was
270 through the UK Brain Banks Network, a coordinated national network of UK brain tissue resources
271 for research purposes [32]. It would be important for neurosurgeons to follow a standard operating
272 procedure (SOP) in order to facilitate the collection of high-quality tissue for the brain banks and so
273 it was proposed to develop SOPs in collaboration with the MRC Brain Bank Initiative and to identify

274 best practice globally. It was also suggested that the Brain Bank Steering Committee engage with
275 cohort principal investigators to encourage them to obtain consent for the use of brain tissue for
276 research purposes. Other suggestions included encouraging pre-consenting for people living with
277 dementia in clinical trials for post-mortem brain donation, collaborating more closely with
278 neurosurgeons, and standardising brain tissue processing in order to maintain its usefulness for
279 study (e.g. rapid cooling of excised brain tissue).

280 Finally, dementia research organisations can set the agenda, drive research and encourage
281 collaboration by sharing of information with the wider research community [33]. Pre-clinical
282 biological data can often be difficult to disseminate in an accessible format, due to the unstructured
283 nature of certain data sets, for example omics type data and imaging. Developing solutions for data
284 sharing and accessibility may enable the field to progress at a faster rate.

285 **Summary of recommendations and suggested actions**

286 **4.1** Use an omics-based approach, and others such as imaging, to map resilience and
287 vulnerability by brain region including all cell types to better understand disease
288 processes, characterise disease trajectory, and potentially yield novel targets for drug
289 discovery

290 **4.2** Access to tissue

291 **4.2.1** Generate neurosurgical SOPs to enable research access to excess biopsy tissue
292 and resected tissue from neurosurgery, where undertaken for clinical
293 indications

294 **4.2.2** Encourage pre-consenting for those in trials for post-mortem brain donation
295 and ensure procedures are in place to optimise this process (e.g. enforce
296 procedures to ensure rapid brain cooling at time of death).

297

298 **5. Robust and reproducible target validation**

299 The need to improve validation of potential drug targets

300 Currently only symptomatic treatments for dementia are available. At best, they transiently provide
301 limited cognitive benefit in approximately 40% of people living with dementia, and they have no
302 impact on the underlying disease processes or the rate of cognitive decline [3, 4]. While
303 development of symptomatic treatments has slowed, the search for dementia preventing or
304 modifying treatments has increased significantly [34].

305 A plethora of innovative approaches to drug discovery are emerging, with the identification of
306 putative novel mechanisms and potential drug targets being published in high profile journals.
307 However, robust and reproducible biological validation of potential new molecular targets is key to
308 successful and productive drug discovery. It is critical that exciting early published findings can be
309 reproduced across different model systems and laboratories to provide confidence when moving
310 from laboratory to clinic. However, translating these early novel biology findings into robust drug
311 target validation is often met with failure and there are still many significant barriers to successful
312 drug development. The reasons for this are many fold, including incentives to publish pre-clinical
313 work without the necessary robust evidence for relevance of applicability to human disease;
314 fundamental differences in the biology and degeneration of brain cells in different species; and
315 limitations in the human disease models and outcomes. Incentives to publish novel findings as
316 rapidly as possible detracts from reproducing initial novel findings either within the same academic
317 lab or in independent labs. Grant funding does not always readily allow the reproduction of findings
318 in different *in vitro* and *in vivo* models, and validation data are less attractive to publishers. In
319 addition, the pressure on both academic and biotech researchers to progress targets rapidly to the
320 next stage of development does not necessarily support robustness or establishing cross-species
321 homologies. Whilst these issues are not confined to dementia research, the current paradigm for
322 target validation in neurodegenerative research should be strengthened significantly with an

323 emphasis on both robustness and reproducibility of early preclinical experimental methodology and
324 findings.

325 Significant effort is required to address these issues with emphasis on training and awareness (e.g.
326 scientists trained in pharmacology and rigorous experimental design including robust statistics). High
327 quality collaborative and interdisciplinary proposals should be incentivised, to encourage research
328 groups working on identical/similar targets can share their expertise, minimise risk and cost and
329 improve robustness and reproducibility through integration of diverse disciplines. There was also
330 consensus that incentivising validation of potential drug targets through cross verification from two
331 or more sources, for example bioinformatics data, genetics, cell biology *in vitro* and *in vivo* and real-
332 world observational data would result in significant long-term benefits.

333 The results of an interesting discussion on facilitating reproducibility and robustness of early
334 experimental findings focussed on the expertise of independent grant review. It was proposed that
335 high quality grant review could be achieved by the following: (1) encouraging wider expertise from
336 other fields to participate in the grant peer review process; (2) provide detailed and constructive
337 feedback, which can help researchers better understand how to achieve robust target validation;
338 and (3) use of good practice guidelines that can be shared across the scientific community.

339 Examples of good practice methodology could be collated in order to develop the guidelines for drug
340 target validation similar to the Animal Research Reporting *In Vivo* Experiments (ARRIVE) guidelines
341 [35] or the Organization for Human Brain Mapping's Committee on Best Practice in Data Analysis
342 and Sharing [36].

343 Incentives to researchers have not always supported robustness and reproducibility of data, where
344 tenure and promotion structures have placed great emphasis on novel, high impact research, which
345 may have high impact, but risks unreproducible outputs based on a limited number of experiments.
346 Therefore, the incentive structure and training should be reconfigured to also promote validation of
347 results. It is important to raise awareness and incentivise drug target validation and translation as a

348 critical process of drug development for example, encouraging researchers to conduct experiments
349 that provide predefined 'NoGo' decision endpoints in a research proposal, effectively rewarding the
350 termination of futile lines of enquiry. These proposals could be adopted readily and included in the
351 guidelines for grant applications and could be an additional criterion for review.

352 Wider dissemination of information on ineffective technologies/techniques and publishing of
353 negative results should also be supported. This could be achieved through funders encouraging open
354 research platforms (e.g. AMRC Open Research <https://amrcopenresearch.org/>, Wellcome Trust
355 Open Research <https://wellcome.ac.uk/what-we-do/our-work/open-research>, and Alzforum
356 <https://www.alzforum.org/>) to publish data that might otherwise not be published by peer reviewed
357 journals (e.g. negative data). This would enable more timely 'Go'/'NoGo' decisions to be made, and
358 streamline the translational pipeline.

359 The drug target validation process is at the interface between academia and industry, and promoting
360 better collaboration between the two can lead to a better understanding of the basic science of AD
361 and the requirements for drug development. This will ultimately improve and enhance the validation
362 of novel biological findings. Progress in this area has been made through initiatives such as ARUK's
363 Drug Discovery Alliance and Dementia Consortium [37], as well as the US initiative Accelerating
364 Medicines Partnership - Alzheimer's Disease (AMP-AD) [38], although more needs to be done to
365 expand this and other collaboration models to additional institutions and countries.

366 The translation of laboratory-based findings to clinically relevant therapies is very complex. Pre-
367 clinical testing of potential new therapies for AD and other neurodegenerative disorders relies on
368 effective animal models of disease or disease mechanisms that have both face and construct validity.
369 Whilst all animal models have their limitations, a number of established and accepted
370 pharmacodynamic animal models, based on familial mutations in AD, are now used widely to
371 support dementia research. However, even with these select number of models, there is extensive
372 variability in the design of animal experiments between different research groups. This results in

373 animal models with varying characteristics, which ultimately leads to lack of consistent validation.
374 Compounding the issue, is the lab variability introduced by not using the appropriate background or
375 control strains. To improve validation, optimised experimental design protocols for animal models in
376 dementia should be developed and standardised. This should entail an in depth review of existing
377 models and experimental procedures followed by open publication of standardised animal protocols
378 and promotion of their use (e.g. preference setting by high profile journals and funding bodies),
379 similar to the NEWMEDS initiative for schizophrenia research [39]. Scientists working in
380 osteoarthritis research have recently published ‘considerations for the design and execution of
381 protocols for animal research and treatment’ [40] to complement the ARRIVE guidelines [35], and a
382 guide has also been produced for Huntington’s disease animal models [41]. A similar protocol could
383 be developed and adopted for animal model research in dementia diseases.

384 **Summary of recommendations and suggested actions**

385 **5.1.1** Provide training for scientists in areas of skills gaps (e.g. pharmacology, statistics)
386 and facilitate collaboration

387 **5.1.2** Incentivise validation of potential drug targets through cross-verification with
388 different sources of data and different experimental systems

389 **5.1.2.1** Funders should require robust validation approaches in funding applications,
390 with use of multiple data sources/systems and, where appropriate, use of
391 independent labs

392 **5.1.3** Support the sharing of information on ineffective technologies/techniques and
393 publishing of negative results

394 **5.1.3.1** Funders should encourage open research platforms (such as Alzforum) to
395 publish negative data and the scenarios within which they are tested

396 **5.1.4** Facilitate translation from novel target validation to early drug discovery (e.g.
397 through models such as the ARUK Dementia Consortium, where expert scientists
398 from different sectors work together)

399 **5.1.5** Develop an optimised experimental design protocol for animal model research

400 **5.1.5.1** Review experimental design and methodologies and publicise and encourage
401 use of suggested standardised protocols.

402 **6. Appropriate choice of subject populations for proof-of-concept clinical trials**

403 Who to select for early proof-of-concept clinical trials

404 Between 2002 and 2012, only one compound of 244 evaluated in clinical trials for AD reached the
405 market, translating to an overall attrition rate of 99.6% with 98% of those evaluated in Phase III
406 clinical trials failing to show efficacy [42]. The number of compounds that progress to regulatory
407 review is among the lowest for any therapeutic area [42]. One of the factors often linked to this high
408 failure rate is inappropriate selection of subject populations in early clinical trials, leading to results
409 that fail to translate through to Phase III trials. A key aim of Phase Ib/IIa studies is to show proof of
410 pharmacology over a short period of time, and these trials typically restrict inclusion to a very small
411 fraction of the total pool of people living with dementia (e.g. excluding by common co-morbidities,
412 or narrow stage of disease). Thus, the typical Phase IIa population of people living with dementia
413 may not be representative of the wider cohort that is the likely population to be evaluated in Phase
414 III. For AD it may be beneficial to consider using a more heterogeneous population in Phase IIb trials,
415 to increase the probability of success in the wider patient populations or to restrict recruitment in
416 Phase III trials to a population of patients more likely to benefit from a particular treatment.

417 The current challenge of recruiting appropriate subjects to proof-of-concept clinical trials is complex
418 given the questions that need to be addressed by early stage studies, i.e. safety and proof of
419 mechanism/efficacy on disease progression within a relatively short period of time. For evaluation of
420 an AD therapeutic prodromal AD and/or early AD may not be the relevant populations, as the time

421 taken to show a clear change in cognitive decline is likely to be beyond the reasonable duration of
422 such trials (typically over 18 months), until a time when there is a consensus on more sensitive
423 endpoints. Therefore, in order to effectively demonstrate proof of concept, alternative subject
424 populations could be recruited to these studies, with subsequent studies expanding to include the
425 AD populations. This strategy relies on the true relevance or functional equivalence of the
426 alternative population to AD. Such equivalence is often assumed, but rarely proven. For example,
427 targeting clearly defined populations such as Down's syndrome or familial AD to demonstrate
428 mechanistic efficacy could not only facilitate therapeutic proof of concept but also enable the
429 development of treatments for populations with significant unmet medical need. If proof of concept
430 were to be demonstrated in these groups, trials could then be expanded to incorporate the wider
431 AD population. In both the Down's syndrome and familial AD populations, A β and tau pathology plus
432 the onset of cognitive impairment follows a path similar to that in sporadic AD, but in both
433 populations the onset and progression of the disease is more predictable and homogeneous with
434 less co-morbidity than late onset populations [43, 44].

435 The aims for research and development in recruiting people with Down's syndrome, familial AD, and
436 sporadic AD to a study somewhat differ. People with Down's syndrome represent a population in
437 which to explore the early efficacy of drugs, particularly those targeted against A β and tau, which
438 slow down disease progression. Almost all people with Down's syndrome progress to AD and
439 dementia, with an A β pathology which is very similar to that observed in people with AD [43]. Thus,
440 they represent a population of huge unmet medical need in their own right. In addition, they
441 arguably represent a more homogeneous population where the A β pathology is well defined and
442 where drugs can be evaluated for pharmacodynamic effects and early efficacy at a very early stage
443 in the disease process. The latter is also arguably the case for familial AD. However, one important
444 consideration is that both these populations are different to the majority of people with sporadic or
445 late onset AD: they are younger, more commonly present with phenotypes other than typical
446 amnesic mild cognitive impairment AD and have subtly different neuropathology to sporadic AD

447 and differences in the role of vascular pathology in pathogenesis. In addition, in people with Down's
448 syndrome, the variability in pre-morbid cognitive function raises challenges for outcome measures
449 and informed consent issues, which is not the case in familial AD. These and other differences may
450 compromise the predictability of a drug effect, given the non-equivalence to most people with AD.
451 Even taking this into account, these populations may offer a route to delivering early proof of
452 efficacy for some compounds and should be considered on a case-by-case basis depending on the
453 mechanism of treatment.

454 Alongside this approach, new strategies should be explored to better stratify subjects into clinical
455 trials. There is a requirement to identify, recruit, characterise and allocate people using clinical study
456 registers to create dementia cohorts. One potential solution is using longitudinal phenotyped
457 clinical registries and readiness cohorts, the current strategy of the DPUK (which includes the Deep
458 and Frequent Phenotyping study) and European Prevention of Alzheimer's Dementia (EPAD)
459 Consortium respectively [45, 46]. Furthermore, there is currently very little information on genetic
460 factors linked to the rate of disease progression, or phenotypic variance (e.g. amnesic vs. posterior
461 cortical atrophy vs. logopenic aphasia variants of AD). Large scale and long-term registers allow for
462 people to be profiled mechanistically and longitudinally, including disease progression, to distinguish
463 genetic and environmental determinants of fast versus slow progressors, enabling more accurate
464 stratification for clinical trials. This approach has been informative in Parkinson's disease and
465 frontotemporal dementia [47, 48].

466 Recruitment of individuals to clinical trials remains low even with the existence of many cohorts and
467 the above-mentioned registries. In order to improve recruitment to clinical trials, it is important to
468 understand the barriers and incentives to increase clinical trial participation and to engage with
469 principal investigators to incentivise the use of cohorts. This is one of the priority areas promoted by
470 Bill Gates in his plans for investment in AD [49]. One barrier to increasing clinical trial participation
471 by well characterised subjects within existing cohorts is the mutual exclusivity between longitudinal

472 observational phenotyping over several years and therapeutic studies; these activities do not need
473 to be mutually exclusive, but in practice they often are. To address this issue, it is essential that
474 participation in research is increased so that both types of studies can coexist without mutual
475 exclusion.

476 **6.1. Summary of recommendations and suggested actions**

477 **6.1.1.** Select relevant populations which best address the questions being asked at the
478 relevant stage of development i.e. proof of concept/mechanism/pharmacology

479 **6.1.1.1.** Focus on mechanism/pharmacology/efficacy in clearly defined populations
480 initially to allow demonstration of proof of mechanism/pharmacology and
481 subsequently expand to the wider AD population if appropriate

482 **6.1.1.2.** Examples of such populations could be Down's syndrome or familial AD,
483 where there are huge unmet medical needs, and pathology is sufficiently similar
484 to that of sporadic AD, but disease progression is more rapid or more predictable

485 **6.1.1.3.** Early proof of concept populations could provide the predictive data
486 required to expedite the next phases of clinical development

487 **6.1.2.** Consider how to improve genotype-phenotype translation to enable stratification of
488 people living with dementia for clinical trials

489 **6.1.2.1.** A longitudinally phenotyped experimental medicine register could facilitate
490 this

491 **6.1.2.2.** Profile people living with dementia mechanistically and longitudinally along
492 disease progression to better understand the biology/pathology associated with
493 fast and slow progressors to enable accurate stratification

494 **6.1.3.** Understand barriers and incentives to increasing clinical trial participation and
495 incentivise the use of cohorts and registries

496 **6.1.3.1.** Longitudinal observational phenotyped cohorts and therapeutic readiness
497 cohorts are often mutually exclusive but are equally critical for clinical research -
498 increase participation in research to fill both cohorts.

499 **7. Improving approaches to assess drug-target engagement in humans**

500 Making more informed decisions in clinical development

501 Prior to neurodegenerative disease therapeutics entering the clinical pipeline they are screened for
502 their pharmacology, pharmacodynamics, pharmacokinetics and toxicity in preclinical model
503 systems. Data from these studies are intended to inform factors such as safety, optimal clinical dose
504 range, blood-brain barrier penetration and binding to the intended target [50]. Although these
505 preclinical data are informative they do not fully describe all the clinical findings in early human
506 trials. It is therefore important to be able to make more informed 'Go'/'NoGo' decisions early in
507 clinical development and establish approaches to minimise risk and maximise the potential for
508 success as a therapy progresses through the various stages of clinical development [50].

509 Demonstrating proof of target engagement/pharmacology in humans early in clinical development is
510 crucial for reducing the risk involved in progressing novel drug therapeutics from Phase I
511 safety/pharmacokinetic studies to later stage efficacy studies. In other fields, such as psychiatry,
512 ascertaining the clinical pharmacology profile of novel drugs in early clinical development is a
513 relatively common practise (e.g. PET ligand displacement studies) but is often overlooked in
514 neurology therapeutics development, often due to lack of appropriate tools in clinical practice.
515 Instead, compounds are progressed directly from Phase I/Ib safety/tolerability studies into Phase
516 IIb/III efficacy studies. This strategy, particularly used in the narrow focus of the development of
517 therapeutic antibodies, can contribute to poor decision making along the path of dementia drug
518 development and testing leading to unsatisfactory outcomes in costly, late stage clinical trials.

519 If achievable, being able to show drug target engagement and pharmacological consequence at the
520 site of action serves a number of useful purposes: (1) it establishes that the therapeutic reaches and

521 engages the relevant target site of action; (2) determines the relevant pharmacological dose range
522 for moving to later stage clinical trials; (3) it significantly reduces the risk of progressing a drug
523 inappropriately into late stage development; (4) it allows optimisation of dosing regimen based on
524 established pharmacokinetic/pharmacodynamic relationships; and (5) it provides confidence that
525 the mechanistic hypothesis, being targeted by the therapeutic, is truly being evaluated for efficacy in
526 a population of people living with dementia. However, due to the costs associated with this early
527 stage of development (particularly if new tools / approaches are needed) and a need for more rapid
528 therapeutic development, there may be the potential to bypass these studies. Thus, it is important
529 to find more collaborative risk and cost sharing approaches to show target engagement and drug
530 pharmacology as these studies are critical in early drug development. To date, disease-modifying
531 drugs that have reached Phase III clinical trials are primarily either small molecules or
532 immunotherapies that target A β [34]. Behind this wave of A β targeted drugs are those that are
533 directed towards tau [34] including those which reduce tau hyperphosphorylation, tau accumulation
534 or prevent the spread of toxic tau species. The current methodologies that demonstrate target
535 engagement for tau are limited to cerebrospinal fluid (CSF) biomarker measurements, because of
536 current uncertainty over off-target binding of PET ligands, even if heuristically binding of these
537 ligands highly correlates with disease pathology and phenotype [51]. More recently, there has been
538 a focus on targeting various neuro-inflammation pathways and processes. It is important, therefore,
539 to establish methodologies for measuring target engagement or proof of pharmacology across a
540 range of these drug target classes, to facilitate a risk-reduced progression of such drugs to the next
541 stage of development.

542 A second area that is gathering momentum is the measurement of synaptic integrity and health, this
543 can potentially provide a pharmacodynamic endpoint for many different therapeutic approaches,
544 and also has the potential to serve as a relevant diagnostic biomarker. Relevant methodologies
545 include PET approaches for measuring synaptic density, and magnetoencephalography to measure
546 circuit function including changes in oscillations [52]. One example of such an approach is the

547 synaptic vesicle glycoprotein 2A (SV2A) PET ligand (radioligand [53] (UCB-J) which is currently being
548 evaluated as means of quantifying synaptic density. This radioligand ligand has been validated in
549 humans including people with AD [53]. Initial studies suggest this approach may not only provide
550 evidence of target engagement and early proof of mechanistic concept but could provide an
551 approach to assessing prognostic drug efficacy as well as potentially being useful as a diagnostic for
552 neurodegenerative diseases more generally.

553 The discussions in this session focused on how to scope and facilitate collaboration in developing
554 cost- and risk-sharing approaches to demonstrate target engagement, drug pharmacology and
555 pharmacodynamic effects for target class mechanisms e.g. tau or neuroinflammation. This would
556 span different drug approaches across multiple companies/partners. A potential approach is to
557 establish public-private partnerships, similar to the DPUK's Synaptic Health Theme, and the model
558 used by ARUK's Dementia Consortium for early drug discovery projects [7, 37]. The Consortium aims,
559 through a cost-sharing and risk-sharing approach to translate fundamental academic research to
560 early drug discovery programmes for new dementia treatment [37].

561 Regarding the exploration of new methodologies for measuring target-engagement and proof of
562 pharmacology, one area that is underdeveloped in the UK is the sampling of CSF for relevant
563 pharmacological endpoints. CSF is a useful resource in AD, given the breadth of analysis now
564 available, for determining drug pharmacodynamic effects, pharmacology and target engagement as
565 well as assessment of disease biomarkers, tracking disease progression and potentially improving
566 early diagnosis [54]. However, unlike some other European countries, lumbar punctures are less
567 commonly used in dementia clinical practice and dementia research. CSF sampling has recently been
568 included in the updated National Institute of Care Excellence dementia guidelines, also showing the
569 importance of this resource in a clinical setting [55]. Potential solutions to this issue would be to
570 raise awareness of the high tolerability as well as utility of lumbar puncture, within both healthcare
571 providers and the general public. However, it was noted that to achieve success in this area in the

572 UK, it is necessary to understand how to change the culture and training for CSF collections to
573 become a routine procedure.

574 The UK is a major partner in the international development of other new technologies for dementia
575 research, including multiple UK centres participation in the EU Joint Programme -
576 Neurodegenerative Disease Research (JPND) 2016-17 initiative for standardisation and
577 harmonisation of new methods including magnetoencephalography, tau-PET, and ultrahigh field MRI
578 [56]. UK and international support for these initiatives has succeeded in bringing expertise in to
579 dementia research which had not previously been engaged.

580 **Summary of recommendations and suggested actions**

581 **7.1.1.** To scope and facilitate collaboration in developing cost- and risk-sharing approaches
582 to demonstrate target engagement, proof of mechanism and proof of drug
583 pharmacology for drug mechanisms common across multiple companies/partners

584 **7.1.1.1.** Public-private partnership approach, similar to the cost-sharing, risk-sharing
585 approach set-up for ARUK's Dementia Consortium and DPUK

586 **7.1.1.2.** To focus on common mechanisms for drugs currently in late stage preclinical
587 development

588 **7.1.2.** Facilitate the use of CSF sampling to determine target engagement, proof of drug
589 mechanism and effects on pharmacodynamic endpoints

590 **7.1.2.1.** Understand how to change the culture, improve training, and encourage CSF
591 collections to become a routine procedure

592 **7.1.3.** Support advances in translating putative pharmacodynamic endpoints into useful
593 clinical assays.

594

595 **8. Innovative approaches to conducting clinical trials if we are able to detect**
596 **diseases 10-15 years earlier than we do today**

597 How to approach clinical trials differently if detection/diagnosis is achieved earlier
598 The majority of potential AD therapeutics have failed to show efficacy in Phase III clinical trials. At
599 the time of writing, there have been no new drug approvals for treating AD since 2003. A potential
600 reason for lack of efficacious and novel therapeutics in late stage clinical trials is that treatment
601 intervention may be occurring at too late a stage in the disease process. There is widespread
602 agreement amongst experts that if we were able to detect, and ultimately diagnose, disease at a
603 much earlier stage then the chance of successful disease-modification, in addition to symptomatic
604 therapies, would increase significantly. To this end, researchers are looking towards developing
605 tools that will allow early detection, diagnosis and treatment of diseases underpinning dementia at
606 an early stage of disease. As a minimum these tools could help to efficiently and accurately triage at-
607 risk individuals for detailed clinical diagnosis but ideally, they would provide a tool that detects and
608 subsequently diagnoses early stage disease, where perturbation of the disease process itself
609 pharmacologically would have the greatest long-term therapeutic benefit.

610 Several hurdles need to be overcome if such detection/diagnostic tools do become available, not
611 least that the duration of Phase IIb/III clinical trials will increase significantly to allow measurement
612 of clinical efficacy of drugs. Already, with the disease-modifying drugs currently in development, it is
613 a challenge to conduct trials of sufficient duration to demonstrate a difference in the slope of
614 cognitive decline. Early detection/diagnosis will compound this issue if existing cognitive outcomes
615 retain primacy as measures of a beneficial effect, as trials will be required to run for even longer
616 periods. If we are able to reliably detect/diagnose 10-15 years earlier, innovative approaches to how
617 late stage clinical trials are conducted and implemented will be necessary which may include novel
618 cognitive outcome measures more sensitive to neurodegenerative changes at their earliest phase
619 [57]. Regulatory bodies are looking to provide conditional approval of dementia drugs based on

620 surrogate markers which may enable alternative means of collecting Phase III clinical trial data in a
621 'real-world' setting utilising memory and brain health clinics for data collection [58]. This would
622 allow for passive and active monitoring remotely using standard clinical endpoints but also digital
623 approaches, generating 'real-world' data. To address this, a community-based trial protocol is
624 currently being developed by ARUK to provide an exemplar of conducting real world (e.g. memory
625 clinic-based) pivotal clinical trials for AD ('virtual' clinical trial). To achieve this, there needs to be
626 increased engagement with regulators to inform guideline development and regulators need to be
627 persuaded of the value of a virtual clinical trials approach.

628 An alternative and complimentary strategy is to develop more sensitive tools for detecting cognitive
629 change that can be used at-scale. Many outcome measures use well established technologies that
630 have been developed for use specifically in a clinical context. These measures are unsuitable for use
631 in large pre-clinical populations. A strong case can be made for a new generation of digital cognitive
632 phenotyping tools that can detect early changes indicating increased clinical risk. This is an
633 opportunity for stakeholders to collaborate in developing standard tools that are understood and
634 accepted by regulators, industry, and academia.

635 If it is possible to detect AD much earlier than current methods allow, an important factor to
636 consider is the impact for individuals who have the disease detected and their families. Current trials
637 use different outcome measures (clinical, functional and biological) to determine the efficacy of the
638 treatment, however these outcomes have not been determined patients and their carers but are
639 instead an objective measure of clinical symptoms. Therefore, it will be extremely important to
640 understand the preferred outcomes of people living with dementia for early stages of disease, which
641 can then inform drug development and provide additional endpoints for clinical trials. To this aim,
642 ARUK has begun to explore an outcomes project in collaboration with researchers, people affected
643 by dementia, clinicians, and regulators [59]. It is important to continue supporting projects to
644 understand the outcomes people living with dementia prefer and persuade both the research

645 community and regulators of the importance of these in informing clinical trial design and conduct.
646 The AD community are not alone in facing these issues. The EU JPND supported a cross-disciplinary
647 working group, the Presymptomatic Neurodegeneration Initiative, where researchers, funders and
648 regulators considered analogous challenges in AD, frontotemporal dementia, motor neuron disease,
649 Huntington’s disease and other conditions [60].

650 Conducting longer clinical trials will also have implications for data protection regulation. Innovators
651 have patent protection as well as data exclusivity for several years, however, with treatments
652 shifting to earlier stages of the disease and the possibility that patents may not survive for many
653 years after drug approval due to longer clinical trials, there may be a need to evolve data protection
654 regulation and patent life in line with developments in approaches to treatment.

655 **Summary of recommendations and suggested actions**

656 **8.1.1.** If we detect neurodegenerative diseases 10-15 years earlier, propose and
657 theoretically validate a new approach for conducting and implementing late stage,
658 pivotal clinical trials

659 **8.1.1.1.** Develop a community-based trial protocol to provide an exemplar of
660 conducting a real world (e.g. memory clinic) pivotal clinical trial for AD

661 **8.1.1.2.** Engage with regulators and relevant bodies to inform the development of an
662 innovative approach to the conduct of late stage clinical trials including digital
663 cognitive phenotyping strategies

664 **8.1.1.3.** Educate regulators regarding the value of a ‘virtual’ clinical trials approach

665 **8.1.2.** Understand outcomes people living with dementia prefer for early stages of disease,
666 which can inform drug development and provide additional endpoints for clinical trials

667 **8.1.3.** Work with relevant stakeholders to evolve data protection regulations in line with
668 the shift to treating earlier in the disease course.

669 **9. Conclusions**

670 The national and global objective of delivering a disease-modifying treatment for dementia by 2025,
671 as well as the development of improved symptomatic therapies, will require a multi-faceted
672 approach to broaden current research areas by addressing prevention, earlier detection/diagnosis,
673 disease mechanisms and the design of clinical trials. Specific recommendations and actions detailed
674 in this paper include:

- 675 • Using a more integrated biology approach to translate genetic data into cell biology
- 676 • Map resilience and vulnerability by brain region using an ‘omics’-based approach
- 677 • Include requirements in funding applications for robust target validation in pre-clinical
678 models and humans
- 679 • Using multiple data sources to increase reliability and reproducibility of findings
- 680 • Focus on demonstrating proof of mechanism/pharmacology/efficacy in clearly defined
681 populations (e.g. Down’s syndrome) initially and subsequently expanding to the wider AD
682 population
- 683 • Develop cost-and risk-sharing approaches to demonstrate target engagement
- 684 • Developing a community-based clinical trial protocol to promote a paradigm shift in how
685 late stage clinical trials could be conducted.

686 In addition to specific recommendations for individual themes, there were also a number of
687 recommendations that were relevant across all the themes. These include incentivising
688 collaborations both within the dementia field and with other fields, consideration of data sharing,
689 interoperability and centralised databases, promoting and supporting the sharing of research tools,
690 changing the incentives in academia and industry to encourage a more collaborative approach and
691 raising education and awareness of the public, research community and clinicians. The overarching
692 resolution is to find additional ways to incentivise collaboration, particularly interdisciplinary
693 collaboration, to standardise approaches, to re-think clinical approaches to early and late stage

694 clinical trials and to efficiently and comprehensively share data and samples at all levels across the
695 scientific community. All are essential to accelerate the progress towards the goal of developing an
696 effective treatment for AD by 2025.

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701

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