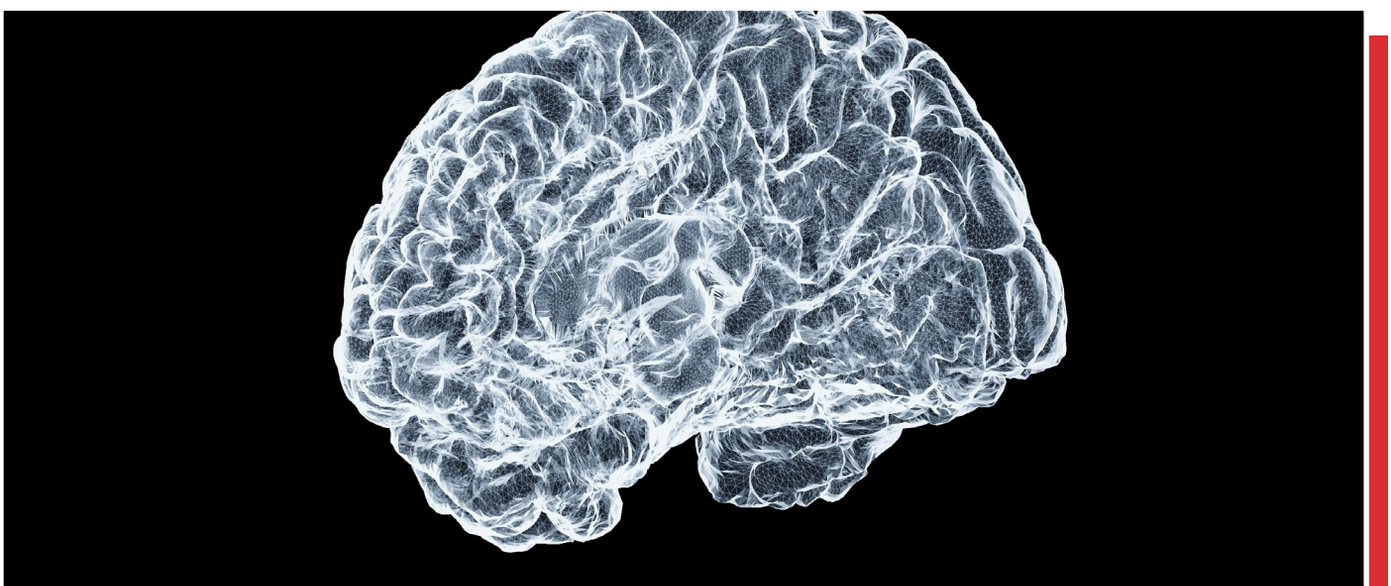
Review

How effective is aducanumab at reducing beta-amyloid plaque in Alzheimer's Disease?

Sareena Khan
Year 2, Medicine, University of Exeter
Email: sk916@exeter.ac.uk



Abstract

Alzheimer's Disease (AD) is a widespread fatal neurodegenerative disease. Evidence suggests toxic beta-amyloid, which is produced in the brain, aggregates into plaque unique to Alzheimer's, which causes symptoms commonly associated with AD. No cure exists, creating an urgency to design drugs targeting the disease's pathophysiology. Aducanumab shows promise in plaque reduction. This is monitored using biomarkers, functional imaging and cognition scoring. This review aims to evaluate the effectiveness of aducanumab at reducing beta-amyloid plaques, by considering change in biomarkers, position emission tomography (PET) results and cognition. When observed using amyloid biomarkers to detect plaques, studies show aducanumab is effective at reducing plaques at certain doses. This is supported by studies using PET scans to visualise and assess plaque levels. These results were statistically significant and applicable to the wider population. However, studies disagree on cognitive findings, remaining unclear about the extent of clinical benefits of aducanumab, and the link between reducing plaques and improving cognition. Long-term randomised controlled trials are needed to investigate whether there is a correlation between plaque removal and cognition, while evaluating optimal dosing strategies.

Abbreviations

AD – Alzheimer's Disease
Aβ - beta-amyloid
mAb – monoclonal antibody
IgG1 – immunoglobulin G1
FDA – food and drug administration
MCI – mild cognitive impairment
CSF – cerebrospinal fluid
PET – positron emission tomography
Aβ-PET – positron emission tomography for beta-amyloid plaques
CDR-SB – Clinical Dementia Rating Sum of Boxes
MMSE – Mini Mental State Examination
ADAS-Cog13 - Alzheimer's Disease Assessment Scale-Cognitive Subscale
RCT – randomised controlled trial
PV3 – protocol version 3
PV4 – protocol version 4
ARIA – Amyloid Related Imaging Abnormalities
ApoE – apolipoprotein E

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease destroying memory and thinking skills and, over time, the ability to perform everyday activities.[1] It is the most common form of dementia in the UK.[2] More than 6 million Americans live with AD, and by 2050 this is expected to increase to 13 million.[3] Currently there are no curative treatments, and previous treatment focuses only on reducing and managing symptoms, not modifying disease pathology,[4] which is why drug development is so important in treating and potentially reversing the disease.

Evidence supports the amyloid cascade hypothesis. This is where toxic beta-amyloid protein (Aβ) is produced in the brain in soluble monomer form, which then aggregates into larger molecules, including soluble oligomers then protofibrils, until insoluble fibrils are formed which accumulate into plaques;[5] this is one of the characteristic pathologies underlying AD.[5] These plaques reduce the ability for synaptic transmission, causing neurones to shrink and die,

which contributes to symptoms. The most neurotoxic form is Aβ42, which is most likely to form plaque.[6] This pathway can be targeted by monoclonal antibodies.[5]

As such, aducanumab is a recombinant human monoclonal antibody (mAb), so binds selectively to a specific target. Aducanumab is a humanised immunoglobulin G1 (IgG1) molecule.[7,8] It is derived from a blood lymphocyte library collected from a healthy donor population of elderly individuals who exhibit slow or absent cognitive decline.[9,10] The mechanism of action involves binding to both aggregated soluble Aβ oligomers and insoluble fibrils to cause plaque removal, since the monomers are non-neurotoxic.[11–13] Aducanumab is the first Food and Drug Administration (FDA) approved anti-amyloid mAb. It is widely tested in early stages of AD, primarily in mild to moderate cognitive impairment (MCI) due to AD or mild Alzheimer's dementia.[12]

Consequently, aducanumab's effectiveness can be measured in numerous ways, including via biomarkers. A biomarker is a measured characteristic indicating normal biological or pathogenic processes, or responses to an exposure or intervention.[14] A pharmacodynamic biomarker measures change in disease progression by assessing response to therapeutic agents.[15] The main Aβ biomarker is an Aβ isoform, Aβ42, which is present in cerebrospinal fluid (CSF) and plasma.[16] An inverse relationship exists between Aβ42 levels in CSF and plasma, and the number of amyloid plaques,[16] because there is less soluble Aβ42 as it has aggregated into fibrillar state in plaques.

However, because biomarkers alone are not enough to provide substantial evidence of plaque reduction, both biomarkers and imaging are used together to evaluate plaque reduction.[17] One imaging form used is positron emission tomography (PET) for beta-amyloid plaques (Aβ-PET). By using radioactive pharmaceuticals that bind to insoluble Aβ fibrils,[18] plaques become visible in imaging.

Although reducing plaques is useful, an important feature of drugs is clinical efficacy. This is quantified by cognitive assessment, which is achieved by multiple scoring systems to assess severity of disease and symptoms. These measure thinking abilities such as memory, language, reasoning and perception, which are some of the symptomatic areas affected in this disease.[19] The primary method is Clinical Dementia Rating Sum of Boxes (CDR-SB). Other methods include Mini Mental State Examination (MMSE), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog13). This review aims to evaluate the effectiveness of aducanumab through its reduction on Aβ plaques, by considering biomarkers, PET imaging and cognitive effects.

Methods

Both Medline (PubMed) and Web of Science databases were searched. The search string used was as follows: (anti-amyloid beta protein drugs) OR (amyloid beta) AND (monoclonal antibodies) OR (MAB) OR (amyloid plaque) AND (Alzheimer's) AND (Aducanumab). Randomised controlled trials (RCTs) and clinical trials were included, and papers published before 2018 were excluded, to ensure recent up-to-date research, yielding three primary studies after screening against irrelevance and incongruent endpoints. Other sources were retrieved using reputable websites, PubMed, and systematic reviews. **Figure 1** illustrates the process of primary evidence synthesis.[20]

Results and discussion

Biomarkers

A study by Ferrero et al investigating both pharmacodynamics and the effect of aducanumab on plasma biomarkers reported no significant effect on plasma Aβ levels between the minimal dosage (0.3mg/kg) and maximally tolerated dosage (30mg/kg).[21] This is consistent with aducanumab's very low affinity for binding soluble monomeric Aβ,[21] since it specifically targets oligomers and fibrils and not monomers. It also reported an increase in Aβ42 at the maximum dose given (60mg/kg). A later study by Biogen called EMERGE investigated biomarker effects as secondary and tertiary outcomes as part of a sub-study.[22] They reported statistically significant changes across the secondary endpoints of biomarkers. The biomarkers displayed dose-dependent increase in CSF $A\beta_{1-42}$ levels. The same results were observed in Biogen's identical study [22] ENGAGE. This suggests that aducanumab is binding to the soluble Aβ, leading to increased Aβ plasma concentration due to the stabilisation of circulating peptides.[23] All studies included[21,22] were randomised, double-blind, placebo-controlled trials, reducing bias in allocation and maintenance. However, a limitation is the subset of participants was not randomised, since the participants chose to opt-in to further sub-studies.[22] The study by Ferrero et al[21] had a small sample size of 53 with one participant withdrawing, however, at the maximum dosage administered, the increase in Aβ may be due to small sample size; this cohort demonstrated higher baseline values and patient variability than those with lower dosage,[21] so results may be positively skewed. However, despite the other studies[22] having a larger sample size overall, the biomarker sub-study tested 78 patients in EMERGE and 53 in ENGAGE,[22] which is a small sample size, not greatly aiding validity and reliability. Despite limitations, these outcomes provide supporting evidence for each other, suggesting aducanumab can reduce amyloid plaque levels. All three studies support each other's findings at a high dose level, however, classification of 'high dose' varies, with Ferrero et al's being higher than Biogen's. Ferrero et al show no significant effect at lower dose, but Biogen's show significant plaque reduction at their higher dose, suggesting multiple doses above 10mg/kg are most effective.

PET amyloid burden

Both EMERGE and ENGAGE recruited individuals with AD with MCI due to Alzheimer's or mild AD, aged 50-85, with confirmed amyloid pathology via PET scan.[22] They tested longitudinal amyloid imaging via PET scan. Both reported dose and time-dependent reduction in the amyloid burden shown on the PET scan. For EMERGE, the mean difference from baseline between high dose and placebo was -0.278 (95% CI, -0.306 to -0.250; $P<0.0001$), and for ENGAGE, it was -0.232 (95% CI, -0.256 to -0.208; $P<0.0001$).[22] The 95% CI for both studies is negative, suggesting a definitive reduction in amyloid burden compared to placebo cohorts. The very small p-values suggest there is strong evidence that, in this study, the mean amyloid burden in the intervention arm is not the same as the control arm, after 78 weeks. The sample size in these sub-studies was larger than the biomarker sub-studies, increasing the generalisability of this data; 488 and 585 participants in EMERGE and ENGAGE, respectively.[22] This reinforces that aducanumab is effective at reducing plaques. Two statistically significant results demonstrate concordance among both studies, however, the identical nature of the studies must be taken into account when drawing conclusions. However, when used with biomarker results, results from PET imaging can confirm conclusions drawn from biomarkers.

Cognition

Ferrero et al also investigated cognition. They documented no dose-dependent response or effect observed in the change of mean ADAS-Cog13 scores from baseline, suggesting no cognitive improvement.[21] EMERGE met its primary endpoint for CDR-SB, reporting 22% reduction in decline for high dose compared to placebo. Furthermore, all cognitive endpoints showed less cognitive decline compared to placebo, reporting across MMSE and ADAS-Cog13.[22] However, data from ENGAGE contradicts these findings, with an increase in cognitive decline in CDR-SB, of 2% vs placebo. This is supported by the secondary findings for MMSE and ADAS-Cog13, being not statistically significant.[22]

The study by Ferrero et al was single dose, with the highest safe and tolerable dose being 30mg/kg.[21] EMERGE was a phase three multi-dose trial. Participants received 20 doses of either high dose 10mg/kg, low dose 6mg/kg or placebo, in a 1:1:1 ratio over 76 weeks.[22] The differences in results may be explained by the difference in dosage

and dosing intervals; EMERGE delivered a lower dose in multiple doses at regular intervals over a longer period, whereas Ferrero et al's delivered a higher single dose.[21,22] This suggests multiple lower doses are more effective at improving cognition.

Two protocol adjustments were made in both EMERGE and ENGAGE during the trials that allowed more participants to receive the maximum dose. Protocol version 3 (PV3) allowed participants who had to suspend treatment due to adverse effects of Amyloid Related Imaging Abnormalities (ARIA), to resume dosing at the same dose and continue titration to the target dose, instead of resuming at a lower dose. Protocol version 4 (PV4) targeted apolipoprotein E (ApoE) ε4 carriers. This is a variant of the ApoE gene that increases the risk of developing AD and other dementias.[24,25] This increased the dose for carriers to the same target dose as non-carriers. Since nearly two thirds of participants were ApoE4+ carriers, PV4 had the greater potential to impact more individuals.[22] However, Biogen claim these adjustments were of greater benefit to EMERGE patients since it started one month later than ENGAGE and enrolled more individuals after each amendment.[22] This may explain the differences in results between the two trials, since more EMERGE participants received a higher dosage. The differences in the cognitive results appeared to violate pre-determined futility criteria, since the two trials appeared to be displaying different results, and so both trials were ended prematurely. However, it was later determined that statistical analysis had been done incorrectly and so results up until the day before futility was declared were used. Since the results were taken still under double-blind conditions, validity remains unaffected.[22]

Biogen's studies, however, had a much larger cohort than Ferrero et al's, of 1638 and 1647 respectively. With these taking place at 348 sites in 20 countries,[22] this setting provides external validity, meaning the results are more likely to be applicable to a broader demographic. However, the mean number of participants per site was nine, which is a very small sample size so is not representative of the population surrounding each site. They[22] are also more representative of the global population than the earlier study.[21] Despite all three studies having a majority of White participants,[21,22] EMERGE and ENGAGE have 74–80% White participants in each cohort,[22] whereas Ferrero et al's study has four dosage groups at 100% White participants, and the others between 67–93%.[21] EMERGE and ENGAGE therefore had a higher proportion of non-White participants compared to the other,[21,22] therefore offering greater representation of the different populations.

Cognitive screening tests are widely used to assess Alzheimer's staging, severity and changes, however, each have their own limitations.[29] The ADAS-Cog tests, such as subtype ADAS-Cog13, has limited utility in MCI, as there may be little cognitive decline to detect. This may affect the ability of the test to detect change so early on and may be insufficiently responsive for trials with MCI.[26] Confounding variables are hugely present in the MMSE. Intellectual disability, educational level, cultural differences, physical problems, and language or speech problems can all affect the absolute score, relying upon factors other than memory.[27–29] However, since this is being used to track a trend, the influence of the test itself on the overall outcome of the study becomes largely irrelevant. The CDR-SB is obtained by interviewing both patient and care partner,[30–32] which increases reliability and provides sociocultural context and baseline function, although this is of questionable relevance when tracking trends.

The disease and symptoms of AD are not solely due to Aβ plaque deposition.[33] Plaque deposition leads to hyperphosphorylation of tau protein, causing protein misfolding and aggregation within neurons.[33] This forms neurofibrillary tangles, which is another characteristic feature of AD.[33] Theoretically, the reduction in plaques seen with aducanumab treatment should reduce hyperphosphorylation of tau, and therefore should cause downstream effects on cognition. As such, any changes in tau tangles, which are also multifactorial, could act as confounding factors for changes in cognition. Additionally, consideration needs to be given to the rates at which plaques are synthesised and deposited, their removal by aducanumab, and their net deposition. Other confounding factors include aducanumab safety considerations, such as treatment-related adverse events, like ARIA.[3] These encompass neuroinflammatory changes such as interstitial vasogenic oedema or sulcal effusion, (ARIA-E), and microhaemorrhages, and haemosiderin deposition, (ARIA-H)[34] which in turn, may alter cognition.

The studies demonstrate variation in cognitive results. The differences between Ferrero et al's study and EMERGE suggest multiple doses of 10mg/kg are more effective than a single 30mg/kg dose, however, ENGAGE data contradicts this. Nevertheless, this does not provide convincing evidence that the drug is ineffective as there is no accounting for confounding variables, differences in patient cohort or protocol adjustments impacting the trials differently.

Conclusion

Aducanumab is proven to be effective, as recognised by FDA approval. Studies show it removes Aβ plaques, demonstrated by an increase in CSF biomarkers, indicating plaque reduction. Both EMERGE and ENGAGE agree aducanumab is effective at reducing amyloid burden on PET imaging, supporting biomarker conclusions. Variation is observed in cognitive results.

Aducanumab is therefore shown to be quite effective at reducing Aβ plaques in early AD and demonstrates potential to exhibit cognitive improvements. However, there is no clear relationship between the extent of plaque removal and cognitive improvement. Longer-term RCTs should be conducted to correlate plaque removal and cognitive improvements, whilst considering regression to the mean and confounding variables. In addition, different dosing regimens should be trialled, from single to multi-dosing, low to high dose and frequency of dose, to find optimal dosing strategies for clinical outcomes in consideration with safety profile.

Since this review was conducted, Biogen have announced aducanumab will be discontinued and are reprioritising resources for further drug development.[35] This decision had nothing to do with efficacy or safety concerns.[35] Aducanumab has laid the groundwork for further research and has paved the way for a new class of drugs.[35] The principles of this drug have been refined in the form of lecanemab, a similar mAb.[36] Building upon selective Aβ targeting, lecanemab has a higher affinity for toxic protofibrils than aducanumab, the most toxic amyloid form.[36,37] Plaque removal has been honed and can now remove plaque much more quickly, and even prevent deposition of plaques.[37] Safety has also been improved, with a lower incidence of ARIA.[37] These advances would not have been possible without the foundations laid by aducanumab, and the potential it demonstrated, and so even though aducanumab is unlikely to be continued, its benefits will have long lasting impacts in future research.

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Sareena Khan

Sareena Khan is a second-year medical student at the University of Exeter. She has an avid interest in public health and global health policy, focusing particularly on health inequalities. She is very passionate about obliterating the gender inequalities that exist for women, particularly in cardiovascular health. She presented this article in poster form at the INSPIRE conference this year and also delivered an oral presentation on another poignant topic. She is a firm believer that passions outside of medicine should be explored, and so in her free time she loves to paint, play golf, and explore the Cornish coastline.

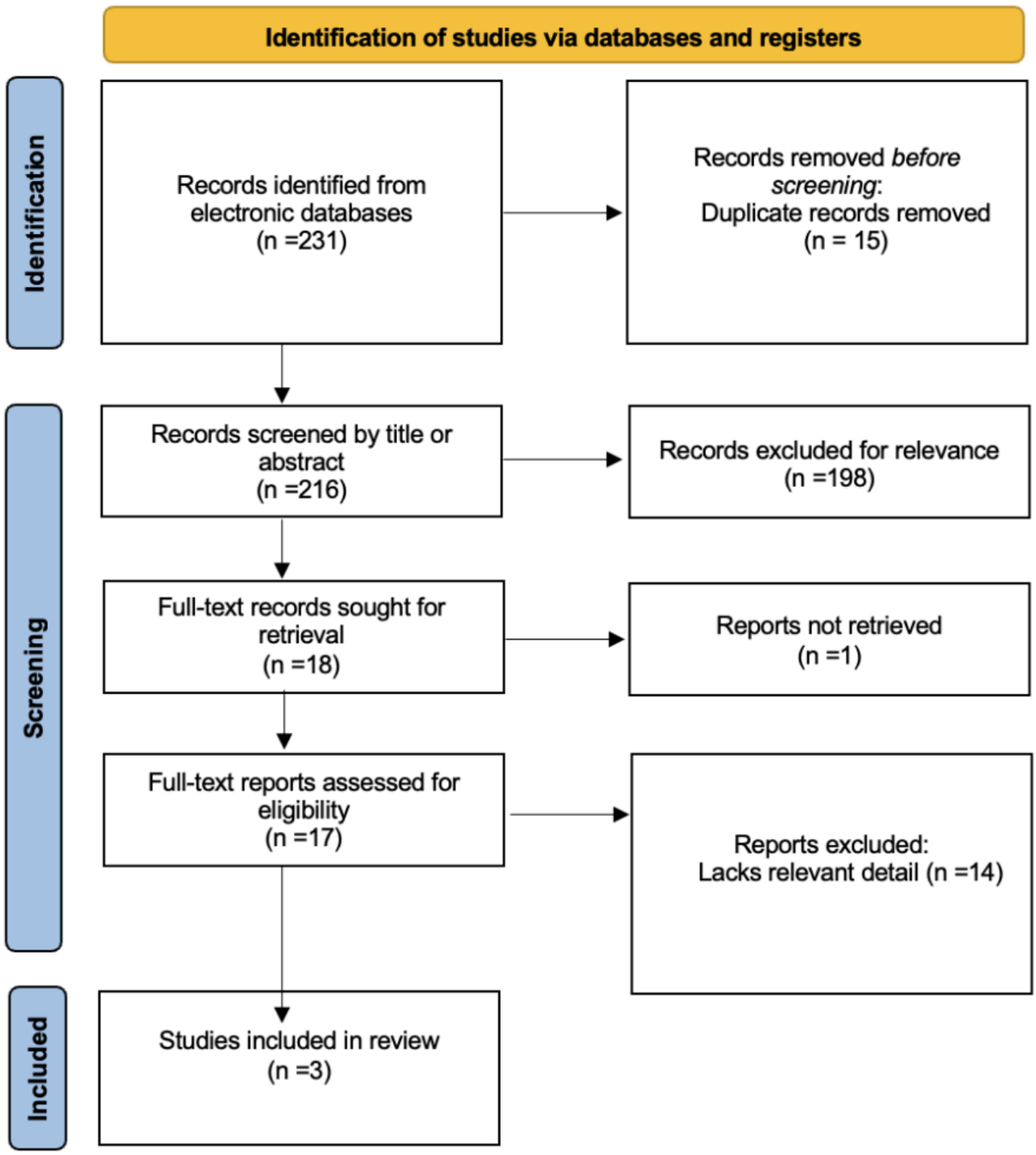

Figure 1. PRISMA diagram outlining primary evidence literature synthesis for this review. This PRISMA diagram has been adapted from the BMJ Prisma 2020 Statement.[20]