Written evidence submitted by the British Pharmacological Society to the Good Clinical Trials Collaborative call for evidence on new guidance to promote and enable good Randomized Controlled Trials

About us

The British Pharmacological Society (BPS) is the primary UK learned society concerned with research into drugs and the way they work. The Society has around 4,000 members working in academia, industry, regulatory agencies and the health services, and many are medically qualified. The Society covers the whole spectrum of pharmacology, including laboratory, clinical, and toxicological aspects. Pharmacology is a key knowledge and skills base for developments in the pharmaceutical and biotech industries, and is therefore fundamental to a thriving UK industry and R&D. These skills allow members of the Society to identify therapeutic areas of clinical need, develop novel treatments that target these areas and ensure these new treatments are incorporated into healthcare practice bringing benefit to patients. The Society publishes three scientific journals: the British Journal of Pharmacology, the British Journal of Clinical Pharmacology, and Pharmacology Research and Perspectives.

Executive summary

The Society supports the Good Clinical Trials Collaborative's (GCTC) new guidance for good randomized controlled trials (RCTs). The suggestions made are reasonable and cover a wide spectrum. RCTs are by far the best tool we have to assess whether a medicine works or not. Trials such as RECOVERY[1], developed due to the COVID-19 pandemic, have further highlighted how important RCTs are and what a difference they can make to patients and public health. This guidance is crucial and is important for all those who undertake RCTs, be that pharmaceutical companies or clinical researchers within hospitals and universities.

As a general comment, we would like to highlight that a lot of current guidance assumes the development of a novel chemical entity (NCE), but RCTs are also used for drug repurposing (with established compounds) and for other modalities such as biologics, devices and cell and gene therapies. Furthermore, this guidance assumes it's a phase III study. However, it is important to note that phase II studies are often RCTs too, and some phase IV studies are also RCTs, and thus the authors should consider expanding the scope of the guidance.

Our main submission on specific sections of the guidance where we feel further explanation or clarification is needed.

Main submission

1. Appropriate trial population

1.1 Historically, a disproportionate number of participants in clinical trials (this is not restricted to RCTs) have a predominantly European ancestry and are male[2]. However, as reported through a growing number of studies, the way in which a person responds to, and is impacted by, a particular drug can vary based on the individual's sex, genetic ancestry, and age (even if not explicitly, often indirectly through comorbidities)[3,4,5]. The elderly have frequently been

[1] RECOVERY trial. Available at: https://www.recoverytrial.net/ (Accessed 3 September 2021).
[2] Bentley, A.R., Callier, S.L. & Rotimi, C.N. Evaluating the promise of inclusion of African ancestry populations in genomics. npj Genom. Med. 5, 5 (2020).
[3] Financial Times (2019) How to stop a lack of diversity undermining clinical trial data. (Accessed 21 October, 2020).
[4] Franconi F, Campesi I, Colombo D, Antonini P. Sex-Gender Variable: Methodological Recommendations for Increasing Scientific Value of Clinical Studies. Cells. 2019;8(5):476. Published 2019 May 17. doi:10.3390/cells8050476
[5] Docherty, J., Stanford, S., Panattieri, R., Alexander, S., Cirino, G., George, C., Hoyer, D., Izzo, A., Ji, Y., Lilley, E., Sobey, C., Stanley, P., Stefanska, B., Stephens, G., Teixeira, M. and Ahluwalia, A., 2019. Sex: A change in

excluded in clinical trials through very restrictive exclusion criteria, or without taking into account of their specific needs, despite the fact that the drug being trialled may be used predominantly in an elderly population. Therefore, the needs of many patients are not being fully accounted for by research.

1.2 The earliest phases of development assess safety. It is critical to have good safety information for the population in which the drug will be used, but in practice these studies tend to be done in young, male and healthy populations. This is partly because the simplest route to running studies as safely as possible is to take steps to minimise risk through setting exclusion criteria. Such criteria relate to factors such as kidney and liver function, weight and smoking – and this will have the effect of focusing the study population around younger participants and those deemed to be healthier and therefore lower risk. Further, the intensity (i.e., overnight stays and follow up visits) and location (mostly cities and near universities) of early phase studies also narrows the population to those who are able to take part – from a health perspective, but also from that of job commitments, caring responsibilities and ability to travel. Also, a more homogenous population is often preferred from the researcher's perspective on the premise that this reduces variability and can therefore deliver clearer proof of concept, while exposing fewer people to a relatively new chemical entity with limited clinical data. In combination, this means many people who should be involved in clinical trials (because they are part of the relevant patient group) are marginalised. The Society recommends that following establishment of dose in young and healthy populations, follow up safety studies to assess dosing in the target population (older people, pregnant and lactating women) should be mandated – for example assessing safety in older people by developing a geriatric or elderly investigation plan that mirrors the paediatric investigation plan.

1.3 We agree that eligibility criteria should be tailored to the question the RCT sets out to answer. Stating that the research is evidence-based and focused on the target patient population could be a useful addition to the section 'including a range of participants but recording key characteristics for them, it will be possible to assess whether there are material differences in the effect of an intervention between such groups.' This will avoid tokenism while also ensuring the appropriate population are being considered. Strategies to improve inclusion, whilst maintaining scientific rigour and patient care are urgently needed if research and the development of medicines is to be relevant to all those who require it.

2. Relevant outcomes and working in partnership with people and communities

2.1 It will be important to ensure that there is evidence that the outcomes of trials are relevant to the target patient population. This is where patient public involvement (PPI) comes in. We want to know what the outcome means for the patient as when we design studies, we are looking for things that are measurable and objective e.g., a researcher might want a 50% improvement in pain score, but what does this mean for the patient? Does this include quality of life for the patient? Patient reported outcome measures should be considered as part of the trial design. Additionally, patient questionnaires can also be useful as they give qualitative information and will also contribute to the completeness of follow-up. However, there must also be a balance - patients must not be overburdened with too many questions. Alongside this,

our guidelines to authors to ensure that this is no longer an ignored experimental variable. British Journal of Pharmacology, 176(21), pp.4081-4086.

in the section titled working in partnership with people and communities, the guidance notes that 'patient and public involvement can play a key role in refining and prioritising research questions; assessing RCT acceptability and feasibility; selection of outcomes that are relevant and meaningful to the intended population; developing the RCT design and procedures; optimising the nature and delivery of information; and encouraging dialogue about access to healthcare interventions that prove effective.' We agree that patients should contribute to defining the questions and agree there is merit in patients playing a role in the design of the study. As we have highlighted, PPI is crucial and what scientists, clinicians and payers may regard as important and relevant may be complemented by other implications they have not considered due to not having the lived experience.

2.2 Patient input on mode of delivery, digital divide and digital fluency are also important to consider. Many trials are now moving to electronic devices and, at a higher-level, there is interest in decentralised remote trials. However, there are certain populations who may not have access to the facilities needed and this needs to be remembered so that all people and communities are considered. Patients need to feel empowered to take control of their health. Technologies could help with this but research into health technology is difficult to interpret. A systematic review, currently in development, and one we can signpost to post-publication, identifies five themes that highlight aspects of remote care which facilitate engagement and should be considered in both future design and trials evaluating remote care technologies used in heart failure. Smart inhalers[6] also have the potential to improve care for asthma by confirmation of the correct inhaler technique and delivery of medicine as well as a measure of adherence in clinical trials.

3. Proportionate, efficient, and reliable capture of data

3.1 In the section that discusses proportionate, efficient, and reliable capture of data, where it mentions 'support privacy and security', this could be further strengthened to 'the security of data capture is important. There must be reliable transfer and it should be ensured that the data cannot be altered'.

4. Adequate RCT size

4.1 A key point when it comes to size is that it depends on the signal (treatment effect) size. In other words, if your intervention makes a big difference, then you will need fewer numbers of patients to predict that difference statistically. As such, large numbers may only be required if effect size is modest. One way to enhance signal size could be to enrich or stratify the population. However, the need for stratification needs to be carefully considered depending on whether the drug is indicated for a wider population (in which case it may lack generalisability) or whether it is a precision medicine. A lot of studies recruit the individuals who are most severe in the disease population because their outcomes are easier to measure i.e., it is easier to see effect of treatment in a severe patient. The guidance on size is appropriate but it needs to be clear that the results apply to that specific population as opposed to the population at large.

4.2 Whereas the statistical power is the primary determinant, there may be additional considerations that also influence size. For example, for a NCE, another key determinant of size for pivotal trials may be the required safety

[6] Asthma UK (2021). Available at: https://www.asthma.org.uk/advice/inhalers-medicines-treatments/inhalers-and-spacers/smart-inhalers/ (Accessed 13 September 2021).

database for registration, which can be a separate consideration from sample size required to demonstrate the primary/key secondary endpoints.

5. Withdrawal from RCTs

5.1 The withdrawal of patients from RCTs is complex. It is fully appropriate that subjects can withdraw from procedures as you cannot compel individuals to carry on in a study if they no longer wish to (but where all/some elements of follow-up such as safety labs still occur), but it's also imperative to have the ability to collect safety and outcome data for those exposed (missing data) as clinicians want to avoid lack of follow-up. It is important to distinguish between discontinuation of study treatment versus withdrawal from the trial (where participants withdraw consent for any additional information to be captured). Clinicians encourage the former over the latter because – as stated in the guidance – removing data can result in unreliable or inconclusive findings, with ethical and clinical safety consequences for both participants continuing in the trial, and the care of future patients.

5.2 As stated in the guidance, if withdrawal is not properly explored, patients may be lost to full or partial follow-up. One of our Society members confirmed that something their clinical research unit ensures is follow-up in the form of a safety visit, which can include bloods and other safety investigations, if participant has withdrawn and left the study. This should be an important addition to the guidance because while there are risks for the study outcomes due to patient withdrawal there is also a patient safety dimension for those who have left.

6. Resources

6.1 We agree that RCTs should not be wasteful of staff and participants' time. Society members who design and work on clinical trials highlighted there is a lot of duplication of systems and equipment; paperwork takes a long time, but then has to be manually inputted; and regulators will often want their information produced in their preferred format. For example, a regulator such as the Medicines and Healthcare products Regulatory Agency (MHRA) will require source data in a specific form. One suggestion is to have a unified paper requirement where agencies like the MHRA and US Food and Drug Administration (FDA) all have the same systems so there is not so much time spent trying to decipher different paperwork systems/requirements. It may be beyond the remit of this guidance to make such a recommendation, but another suggestion is to find a way to streamline certain processes by having an electronic system where trial designers can retrieve the data they need, while also ensuring other aspects of a patient's data are not accessible. This last point is crucial because patient confidentiality is key, but it would also be inappropriate for other health data to be available as that could form a bias for the trial designer.

6.2 Another example given was that of being in an NHS environment. If there is a study related to cancer imaging sometimes certain aspects of the protocol will need to be flexible/pragmatic – i.e., mindful of the clinical environment in which the study is taking place and written pragmatically where possible without compromising the scientific integrity of the study - to adjust for emergencies e.g., making the window 48 hours rather than 24 hours so that emergency cases can use the required imaging equipment as they will have priority over the clinical trial. Another example is, when very specific clinical expertise is required for delivery, (for example, a need for assessments by

dementia experts or psychologists), that their availability is determined and commensurate with the requirements of the trial design.

6.3 It is also important to ensure that systems are tested and processed before the study begins i.e., pressure testing to ensure they will work in practice. One of our members gave the example of a recent First in Human study undertaken with a small biotechnology company. The study had to be paused after recruiting a few patients because the bioanalytical assay used to measure drug concentrations did not perform as expected. The operating characteristics of the assay should have been validated prior to this stage to minimize delays. However, we do not want to be too rigid and there should be allowances for development of non-critical exploratory biomarkers and readouts as part of RCTs.

6.4 As mentioned in the executive summary, the RECOVERY trial is an excellent exemplar of an RCT that has proven to produce results in a time-effective manner. This and the AGILE[7] study are platform studies which have managed to speed aspects of the RCT process up by streamlining certain processes. For example, everyone who has COVID-19 who enters the trial – in this example AGILE – can receive one of 6 or 7 treatments. Any new treatment that enters the trial can then be brought into the existing clinical trial infrastructure. All elements of Platform trials need to be considered in the future because they may not be suitable for all scenarios. Potential challenges could include where the investigational medicinal products (IMPs) are owned by a variety of Sponsors.

7. Safety

7.1 The guidance has several sections that reference safety, which is a crucial aspect of the trials process. Something our members highlighted, which also relates to section 6.1 of this response and the mention of regulator-specific requirements, is that regulators add a lot of complexity around reference safety information. For example, regulators have their own requirements for safety e.g., a battery of blood tests – these may not be necessary clinically, but they may be a requirement for the regulator. It was noted that this is complex for a pharmaceutical development organisation, but close to impossible for non-commercial sponsors to follow accurately. This diverts focus to compliance with the regulations rather than on signal detection, which could ultimately impact the patient and trial.

[7] Agile study. Available at: https://www.agiletrial.net/ (Accessed 3 September 2021).