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EXPERT OPINION

Coping with small populations of patients in clinical trials

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Rare disease research involves small numbers of patients, and this presents challenges in the design, conduct, analysis and interpretation of clinical studies. There are no special methods for coping with small populations of patients in clinical trials; however, there are many different types of clinical study designs and approaches to increase the efficiency and utility of clinical trials. Common to all approaches is the requirement for rigorous planning to ensure that every patient participating in a clinical study contributes as much information as possible. Current approaches aimed at generating the best possible evidence base are discussed, including a focus on regulatory considerations and research initiatives.

Keywords: clinical trials, small populations, study design

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1. Introduction

Investigation of medicinal products requires their safety and efficacy profile to be evaluated in clinical studies. Standard clinical development programmes, which involve large numbers of patients in randomised controlled trials, may not be feasible in certain circumstances. This may occur in the area of rare diseases research, as well as in other areas, such as the paediatric population and in the stratification of more common diseases using biomarker data. Inherent to rare disease research, small numbers of patients in clinical trials present certain challenges, in particular:

- The total number of eligible subjects may be very limited, which impacts the choice of study design and the statistical methodology.
- Challenges in recruiting the necessary number of study subjects, where investigators may 'compete' for the same patient.
- Scarcity of expertise in some disease settings may impact on the ability to conduct the study in all geographical areas.
- The development programme may necessitate the coordination of numerous clinical study sites throughout the world.
- Even if the disease aetiology is known, lack of knowledge of the natural history of the disease may impact on the selection of the most appropriate endpoints.
- Smaller studies are more susceptible to the effects of variability.
- Missing data are likely to be more critical and have a greater impact on the conclusions.
- Greater vigilance is required to ensure that the publication of detailed clinical descriptions does not lead to subject identification.

2. Study design and analysis

Limited numbers of patients present challenges in the design of clinical studies. There are no special methods for coping with small populations of patients in clinical trials, as acknowledged in the Committee for Medicinal Products for

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Human Use (CHMP) guideline [1]. There are, however, many different types of clinical study designs and approaches to increase the efficiency of clinical trials where patient numbers are limited [2-5].

Under the conventional clinical trial framework, the number of patients needed for a particular clinical trial depends on the variability of the endpoint measure in the patient population, the size of the effect to be detected, the nominal significance level for the statistical test and the risk prepared to be accepted by the sponsor of not detecting a difference, if that difference truly exists (translated as the power of the study). In principle, each of these factors might be amended to promote feasibility of a clinical trial, though overoptimistic estimates of target effect size should be avoided. Discussions on which aspect of trial design might be compromised to address limitations in recruitment possibilities are commonplace. By way of example, a nominal significance level of 10% two-sided might be employed in preference to 5% two-sided, in particular where there is high plausibility for a clinical effect based on other evidence (hence the false-positive risk is managed through other means) and low feasibility. This solution may have particular appeal if it means that a clinical outcome measure may be used as primary endpoint in preference to a biomarker, the surrogacy of which may not be well established due to limited epidemiological data. Alternatively, the population may be made more homogenous, or an endpoint with lower variability selected as primary. Of course, if the population for primary analysis is restricted for reasons of homogeneity, a broader population of patients may be recruited to enhance patient numbers for secondary analyses and for assessment of safety – even if the primary analysis for study success/fail is conducted in a pre-defined more homogenous subset [6].

Adaptive study design concerns a statistical methodology that allows the modification of a design element (e.g., number treatments, sample size) at an interim analysis, with full control of the type I error (rejection of the null hypothesis when it is true) [7]. Such a design has the potential to speed up clinical development and can be used to allocate resources more efficiently. A common proposal made by drug developers is to run a conventional Phase II and Phase III design 'adaptively' under the same protocol, with the first-stage results informing some aspect of the design of the second stage. Control of type I error can be achieved for a comprehensive range of adaptations, though in practice adaptations are restricted to assessing variability and hence required sample size, dose or population selection. The study may be 'operationally' seamless, so that conduct is run under one protocol but data are analysed separately, or may be 'inferentially' seamless such that data are merged and analysed for the trial as a whole. The former derives some operational benefits without some of the methodological complications posed by the latter. Inferentially seamless designs may be attractive when patients are scarce, but these types of design present challenges to the sponsor, which include, but are not limited to:

- Operational logistics and feasibility
- Access to the technical expertise needed for appropriate study design
- Dealing with issues of data/trial integrity once interim analyses are conducted
- Concerns over bias in estimated treatment effects

Another methodological topic that merits attention relates to the use of Bayesian methods, which make probability statements on the basis of accumulating data [8]. These are attractive to sponsors since accumulated knowledge may be formulated into a quantitative 'prior' belief to which trial data can be integrated giving an updated 'posterior' (after the trial) belief from which inferences may be drawn; thus, the trial data are not required to stand alone but are integrated with knowledge across the development and scientific literature. One line of thinking is that this type of approach is appropriate to properly recognise uncertainty, in which case the number of patients needed might be increased (the prior is described as 'vague' reflecting uncertainty). More commonly, however, sponsors propose a 'strong' prior meaning that patient numbers may be reduced without apparent weakening of conclusions. There are two main concerns, firstly there is potential that the prior may be constructed in a biased manner favouring a positive outcome to the research question of interest and secondly because the approach results in a single integrated analysis (with assumptions) rather than a series of stand-alone pieces of evidence that may be mutually supportive. Regulatory thinking appreciates the latter – even if usual levels of statistical significance may not be met.

3. Maximising recruitment and retention of available patients

Maximising the participation of eligible subjects is key, where the number of patients in any one country may be small. This can be achieved through international and multicentre collaboration, and active engagement with patient advocacy groups. In addition, specialist centres ensure reliable expert input and diagnosis, facilitating research cooperation through their worldwide networks [9]. Adequate patient education by research staff can also help ensure that the dropout rates and loss to follow up are minimised.

It is inevitable that some data will not be collected and in particular that some patients will not remain on trial until the final protocolled visit, but it is important to minimise the amount of 'missing data'. There is no universally applicable method to deal with missing data, but it is necessary to anticipate the proportion of missing values likely to be observed, to pre-specify the statistical methods and sensitivity analyses that can explore the impact of missing data and to maximise the contribution of each subject through careful planning of data collection and analysis [10].

4. Regulatory considerations and flexibilities

Drug developers have the possibility to seek scientific advice from regulatory authorities, providing input and expertise into the challenges in designing clinical trials, and in particular highlighting potential inefficiencies. In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) has an Innovation Office to help organisations navigate the regulatory processes. The MHRA offers a scientific advice service that can be requested during any stage of development of a medicinal product [11]. In the EU, the Scientific Advice Working Party (SAWP), a working party of CHMP at the European Medicines Agency (EMA), has the remit of providing scientific advice and protocol assistance (special form of scientific advice for designated orphan medicines). The SAWP also runs a procedure for Qualification of novel methodologies for medicine development, giving scientific advice and scientific opinions, for example, Multiple Comparison Procedure–Modelling as an efficient statistical methodology for model-based design and analysis.

Conventionally, multiple pivotal trials are conducted for a marketing authorisation application, but where patient numbers are small a single pivotal trial may be all that is feasible. A CHMP guideline sets out standards to be applied for development programmes that are based on a single pivotal trial but was drafted mainly for more common clinical entities [12]. The principle of the guideline is to increase the hurdle for the single pivotal trial recognising that evidence coming from a single source is inherently less convincing than evidence replicated across multiple sources. However, the challenges of coping with small populations of patients in clinical trials are recognised through flexibilities in the regulatory framework. In order to meet unmet medical needs of patients and in the interest of public health, it may be feasible to grant marketing authorisations on the basis of less complete data than is normally required, for example, conditional marketing authorisation (CMA) and approval under exceptional circumstances in the centralised procedure. An emerging concept is adaptive licensing or 'staggered approval.' Adaptive licensing is based on stepwise learning under conditions of acknowledged uncertainty, with iterative phases of data gathering and regulatory evaluation. The EMA has recently launched an adaptive licensing pilot, which builds on existing regulatory processes. A framework to guide discussions of individual pilot studies has been published and companies that are interested in participating can submit 'assets' for consideration [13].

5. Research initiatives

The challenges noted previously are widely recognised and are receiving attention in methodological research. For example, the European Union has funded three projects to explore new approaches for clinical studies in small populations within the Seventh Framework Programme [14].

- IDEAL: Integrated Design and Analysis of small population group trials. This project aims to explore new methods for the design and analysis of clinical studies and to formulate an effective strategy for assessing clinical trials for rare diseases.
- InSPiRe: Innovative methodology for small populations research. This project focuses on four areas; early phase dose-finding studies, decision-theoretic methods, confirmatory trials in small populations and personalised medicines and use of evidence synthesis in the planning and interpretation.
- ASTERIX: Advances in Small Trials design for Regulatory Innovation and excellence. This project aims to deliver validated innovative statistical design methodologies for cost-efficient clinical trials.

Another recent initiative is the Clinical Added Value for Orphan Drug (CAVOD) study, which aims at setting up the creation of a mechanism for the exchange of knowledge between member states and European Authorities, in order to facilitate informed decision on the scientific assessment of the clinical effectiveness of an orphan drug [15].

6. Summary

High levels of evidence come from well-designed and well-executed clinical trials. In the small populations setting, the most appropriate trial approach will be determined on a case-by-case basis and will depend on the perceived advantages, the disadvantages and what may have to be sacrificed. Whatever the methodology employed, the requirement for statistical efficiency should be balanced against the need for drawing clinically relevant and scientifically robust conclusions. Common to all approaches is the requirement for rigorous planning, to ensure that every patient participating in a study contributes as much information as possible. Involvement of specialist centres can help maximise patient recruitment and ensure reliable expert input.

In the small population setting, the difficulties of designing, conducting, analysing and interpreting clinical studies are recognised and a number of research initiatives are attempting to address some of the methodological challenges. Scientific advice from regulatory authorities can provide expertise into the design of clinical trials and the flexibilities in the regulatory framework such as CMA and approval under exceptional circumstances demonstrate that it is feasible to grant marketing authorisations on the basis of less complete data, though such approaches should generally be considered prospectively.

7. Expert opinion

It is possible to cope with small populations of patients in clinical trials, as demonstrated by the growing numbers of

orphan medicinal products with marketing authorisations. The objective of generating the best evidence base as possible in an ethical and timely manner can be achieved through rigorous planning and early engagement with the regulatory authorities, where discussions to ensure optimisation of the development programme can be fully explored and the acceptability of novel and innovative methodology can be prospectively agreed, for example, modelling and simulation, adaptive designs. Ultimately, there are challenges and compromises to be made in terms of the scientific evidence base for decisions of drug developers, regulators, payers, prescribers and patients. New tools to assist with these challenges are being developed through ongoing research initiatives, aimed at maximising the available resources.

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Declaration of interest

The authors are employed by the Medicines and Healthcare Products Regulatory Agency (MHRA) and are both members of European Medicines Agency (EMA) Committees. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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