Advancing Expansion

The UK is at the forefront of first-in-human clinical trials, with the experiences and results of these being utilised to improve and enhance the implementation of industry guidelines

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The UK has significant experience in first-in-human (FIH) clinical trials and has performed almost a quarter of the total of 2,206 FIH studies in the EU between 2005 and 2017 (Figure 1). Furthermore, the number of FIH trials conducted in the UK continues to increase; 69 out of 143 (48%) Phase 1 trials in 2016 were FIH, whereas, in 2017, this number grew to 105 out of 167 (63%) (1). The collective experience of regulators, clinical Phase 1 units, and FIH principal investigators in the last couple of decades has played a significant role in the development of guidelines for FIH/early phase clinical trials. However, two events come to the forefront of any early clinical developer's mind in relation to the guidance issued by the EMA in this area.

First was the TGN1412 incident at Parexel's Phase 1 unit in Northwick Park Hospital, UK, in March 2006, where all six subjects receiving the first dose of a first-in-class non-breaking-CD28 'superagonist' humanised IgG monoclonal antibody experienced a severe systemic inflammatory response followed by respiratory and renal failure and disseminated intravascular coagulation (subsequently identified as cytokine release syndrome) (2). In response to this incident, the Expert Scientific Group (ESG) – set up by the Medicines and Healthcare products Regulatory Agency (MHRA) to investigate the TGN1412 incident – published a report in 2006 which included 22 different recommendations to improve the safety of FIH trials (3). Many of these recommendations were incorporated into the 2007 EMA *Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products,* which remained the key guideline for the conduct of FIH studies in the EU from 2007 until its revision in 2017 (4).

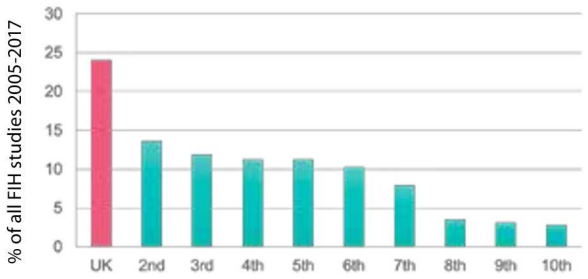

Figure 1: Chart of Top 10 EU member states conducting FIH clinical trials 2005-2017

While an update to the original guidelines was in the planning stage in 2015/2016, the unfortunate event that took place during the combination single ascending dose (SAD) and multiple ascending dose (MAD) protocol FIH trial of the fatty acid amide hydroxylase (FAAH) inhibitor BIA-10-2474 at Biotrial's Phase 1 unit in Rennes, France, in January 2016, prompted expedition by the EMA to publish the revised guidance. This resulted in the incorporation of any deficiencies identified during the investigation by regulators into the factors contributing to the event that resulted in one death and the hospitalisation of four other participants (5-6).

The French Competent Authority (ANSM) set up the Temporary Specialist Scientific Committee (TSSC) to investigate the BIA-10-2474 incident. They noted that the study design had sentinel dosing for SAD cohorts, but not MAD cohorts. The dose escalation was also based on the safety data from the previous cohort, but pharmacokinetic (PK) data only from the last-but-one (n-2) cohort.

The report was published in April 2016 and included six further recommendations to improve the safety of FIH trials. The EMA published a revision to the FIH guideline in July 2017 (7).

2017 Revisions to the FIH Guideline

Much of the 2007 guideline remains in the 2017 revision, with an emphasis on good science and application of pharmacology and toxicology principles. What the revised guideline did introduce was specific recommendations for combination and integrated protocols (eg, combined SAD/MAD/food effect (FE)/drug-drug interaction (DDI), among others).

The revised guidance emphasises that dose selection and escalation should be reviewed based on all emerging human PK and pharmacodynamic (PD) data from previous cohorts and should not be considered fixed based on the original assessment of the nonclinical data. Preclinical or nonclinical PK should be sufficient to support interpretation of the data from *in vivo* PD models to estimate pharmacologically active doses and anticipated therapeutic dose ranges. The key aspect for this is that nonclinical models need to consider both dose and exposure (ie, the levels of drug in the blood) to try and translate to a human scenario.

The other major aspect of the revised guidance of note is that no significant changes were made to the quality of nonclinical requirements for early phase studies. No update was considered necessary to ICH M3 (R2) (the global nonclinical study requirement guidelines), suggesting that the nonclinical studies performed prior to the 2016 incident in Rennes are considered sufficient (8). The interpretation and application of that data has been suggested as a possible deficiency contributing towards the unfortunate events (5, 9). Another aspect that the revised guidelines addressed is the progression from SAD to MAD parts, stating that this decision should be made based on PK-PD modelling where possible. It also stated that sentinel dosing should be used for all cohorts, both SAD and MAD, unless otherwise justified. On day one of the study, sentinel dosing requires that one participant is randomised to active and one participant is randomised to placebo. Both subjects are then observed for a minimum of 24 hours before the remainder of the cohorts are dosed.

> **"The MHRA does not require interim reports to be submitted when moving between different study parts within the same protocol"**

A common enquiry by sponsors following publication of the revised guideline is whether submission of interim reports to competent authorities or research ethics committees are required when moving between the SAD and the MAD parts of the study. The guideline says that this should be considered, but it is not mandatory. For instance, in the UK, the MHRA does not require interim reports to be submitted when moving between different study parts within the same protocol, provided that the decision-making criteria for moving between parts is clearly defined in the protocol.

The conventional components of an early development programme (including SAD, MAD, food-effect, drug-drug interaction, gender effect, thorough QT assessment, and proof of concept [PoC]) would traditionally have been addressed by a separate study and, therefore, a separate regulatory submission, which can be arduous and represents a burden in terms of time and resource. To limit this, over the last decade or so, some competent authorities within the EU became more open to the combination of multiple elements into one protocol and, therefore, requiring only one regulatory submission – the most common being combining the SAD and MAD studies. This was subsequently expanded to include food effect or drug-drug interaction studies, among other components (see Figure 2, page 52).

An additional evolution of early phase protocols that complimented the acceptance of combination protocols was the increasing use of adaptive elements within a protocol. Well-written adaptive protocols allow adjustments to certain elements of the study in response to emerging data without the need for substantial amendment. For example, an important aspect for FIH studies is deciding blood sampling or physiological assessment timings. At the nonclinical stage, it really is educated guesswork, as it is only after data for the first few cohorts is available that we know whether those estimates or timings, particularly for things like PK samples, were appropriate. Having adaptive elements where we have flexibility regarding blood sampling is advantageous and avoids the need for substantial amendments. Likewise, for overlapping or parallel combined studies, specifying in advance after which SAD cohort dosing of the MAD cohorts may commence or after which dose level a food effect is investigated is not necessary. A well-written adaptive protocol will have clearly defined decision-making criteria, which allows this to be flexible.

Risk mitigation remains a key theme within the revised guideline, and, while much remains unchanged in relation to start dose estimation, a welcome addition are some recommendations with regard to the appropriateness of staff and facilities for Phase 1 units that conduct FIH and early phase studies. The guideline notes that facilities should have trained investigators with relevant medical and clinical pharmacology expertise, Good Clinical Practice training, and a clear understanding of the specific characteristics of the investigational medicinal product and of its target mode of action, which are both important when looking at the starting dose calculation.

The study needs to be run in controlled conditions (eg, inpatient care at an experienced, accredited Phase 1 unit), to allow the possibility of close supervision. Phase 1 units do not need to be located within hospital premises, but having the ready availability of an intensive care unit and other hospital facilities, as well as clear procedures in place for transferring patients from the Phase 1 unit to the hospital's intensive care unit, is important. The MHRA is one EU competent authority that has established a specific accreditation scheme for Phase 1 units involved in FIH and early phase research (10). The scheme was, in fact, established in 2007 after the 2006 TGN1412 incident, providing detailed, specific requirements for Phase 1 units undertaking higher-risk (ie, FIH) clinical trials. The scheme is designed to give assurance that accredited units "not only met, but surpassed the basic regulatory GCP aspects by having additional 'best practice' procedures that encompassed the highest standards for avoiding harm to trial subjects and for handling medical emergencies should they arise" (10).

Future Guidelines

The revised guideline is a welcome update, but largely reflects what was already required by many EU competent authorities,

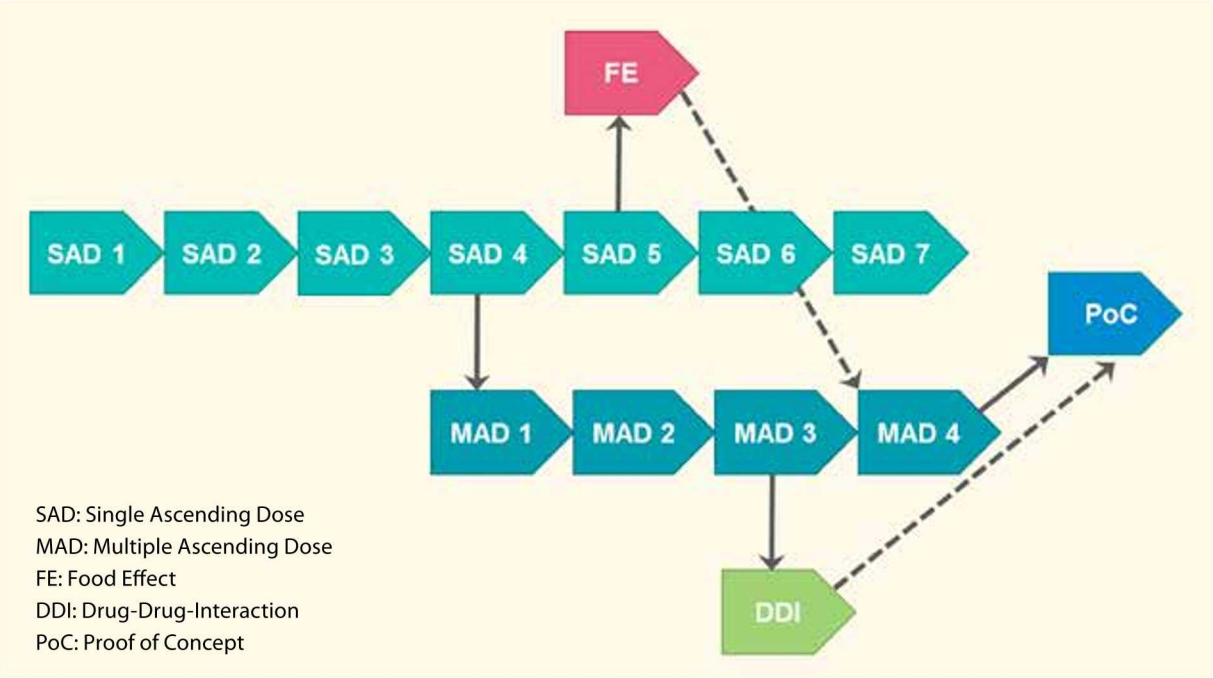

Figure 2: Example of a fully-integrated protocol allowing study parts to run parallel

indeed, being done routinely by many experienced Phase 1 units. The guideline also provides some much-needed clarity on how integrated or adaptive protocols can and should be used effectively, and these can answer many of the early clinical development questions to allow go or no-go decisions.

Remembering that guidelines are exactly that is important – they are not a set of rules that must be followed, and deviations from guidelines are often permissible if they are scientifically justified. Good science and volunteer safety is paramount, and there is an emphasis on the use of emerging data throughout the duration of the study and using this data for informed decision-making for subsequent cohorts and study parts.

In conclusion, if implemented effectively, the revised EMA 2017 FIH and early phase guideline can accelerate early clinical development without compromising the safety and wellbeing of participants.

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About the author

Dr Simon Hutchings has over 11 years of experience in the drug development process, including preclinical pharmacology/toxicology, Phase 1 (including first-in-human) pharmacology/PK studies, and investigator-led Phase 2 and 3 trials. In addition to undergraduate and postgraduate qualifications in pharmacology, he also holds a Certificate in Human Pharmacology from the Faculty of Pharmaceutical Medicine at the Royal College of Physicians, UK. Simon has extensive practical experience and scientific knowledge of the design, management, and reporting of clinical development projects.