



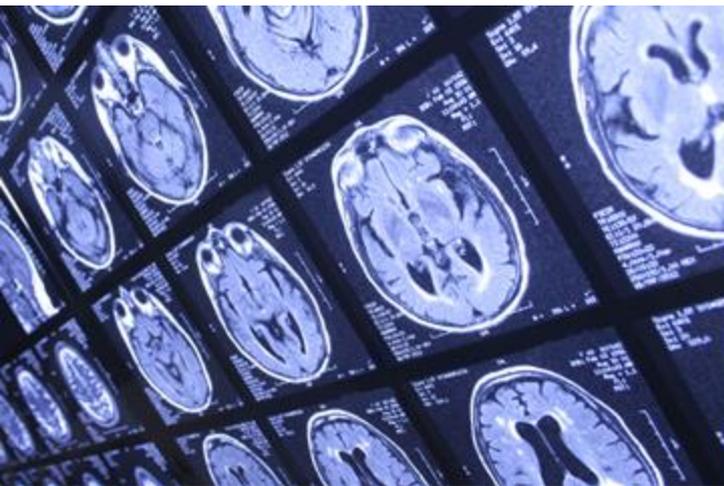
Medicines & Healthcare products
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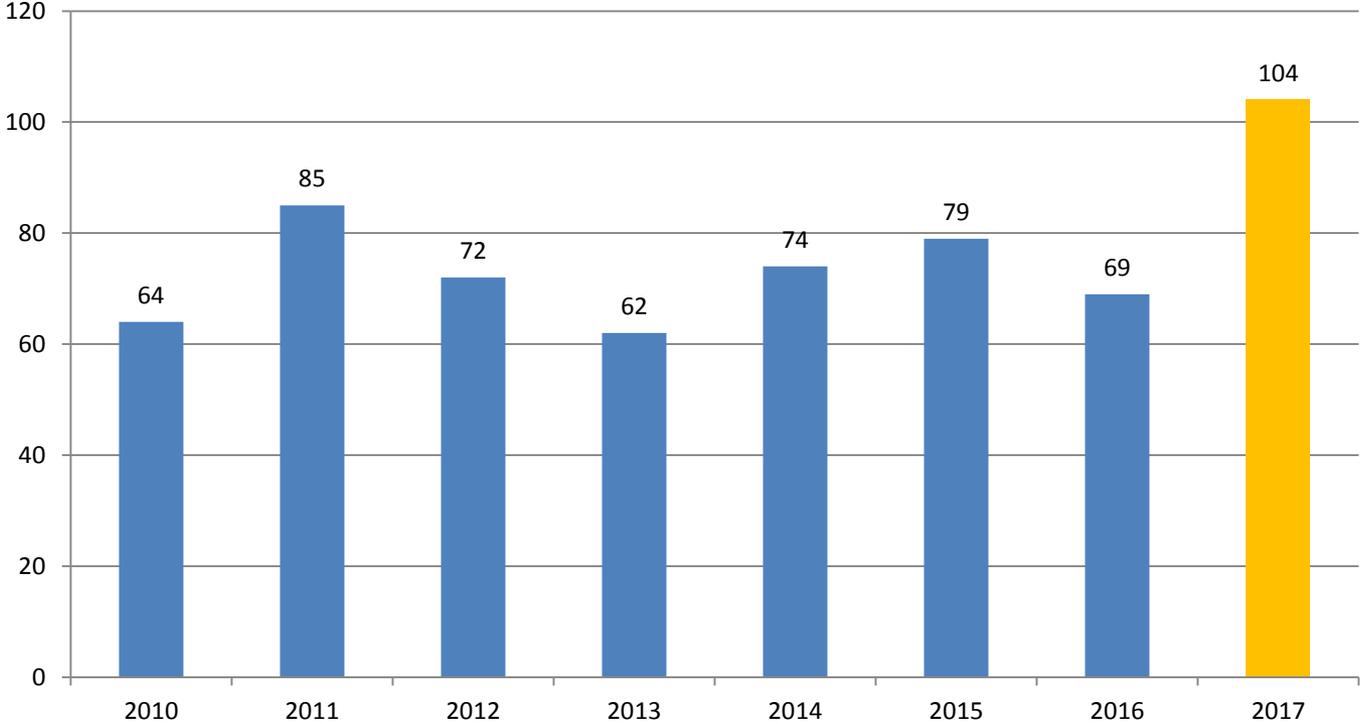
UK Experience of First-in-human trials

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UK First in Human (FTIH) totals by year



20-25% of all FIH trials in the EU involve the UK

Impact of the guideline in the UK

Following implementation of the guidance

- there has been no increase in GNAs (Jan-June 2017 versus June-Dec 2017 and Jan-June 2018)
- there have been no rejections due to non-compliance with the guideline
 - Rejections remain in line with all other phase trials
 - A significant number of rejections were due to the Sponsor not responding to the GNAs at all

Example GNAs - Clinical

- No communication plan for multi-site trial
- No maximum dose or maximum number of cohorts
- Unclear stopping rules – for individual / trial part / whole trial
- Additional stopping rule(s) needed – often serious adverse reaction
- Unblinding rules in an emergency not acceptable
- Poor consideration for drug interactions in a combination therapy or with concomitant medication, including ignoring SmPC risks for marketed products
- Stopping rules – “may” stop not “will” stop, too much flexibility
- Confusing / missing definitions – MTD, MAD, RP2D

Example GNAs – Non-clinical

- Contraception not aligned with CTFG guidance
- Inadequate pregnancy testing
- Dose in healthy volunteers too far above predicted therapeutic range and no justification
- No summary of the analytical assays, and their limits of quantification, used to characterise the nonclinical PK and toxicokinetics
- No confirmation that all pivotal non-clinical were conducted in a country that is a signatory of the OECD Mutual Acceptance of Data (MAD) programme in accordance with the OECD Test Guidelines and Principles of Good Laboratory Practice (GLP).

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Example GNAs - Quality

- Lack of provided data – impurities, retest period
- QP declaration / MA authorisation incorrect or not provided

UK GNA advice

- UK has published on our website “Common issues identified during clinical trial applications”

<https://www.gov.uk/government/publications/common-issues-identified-during-clinical-trial-applications>

- The common GNAs seen in FIH trials are seen across all phases
- It is not our experience that FIH trials have a significant number of GNAs that are specific to requirements of the guideline. The majority are seen across all trials or are trial specific (e.g. based on mechanism of action)
- There is no trend in GNA by product type – SMEs, biologics are all similar

Sentinel subjects

- Not seen universally in all trials
- Lack of sentinel subjects has been accepted in both SAD and MAD trial parts with a suitable justification
- Not aware we have ever requested sentinel subjects are included where the initial protocol has not allowed for this

Adaptive elements in a protocol

UK welcomes adaptive elements in a protocol provided the adaptations are clearly defined and included upfront.

Later adaptations are accepted based on emerging data.

Concluding remarks

- UK did not experience any significant change in submissions or outcome following the publication and implementation of the FIH guideline.
- The survey does not completely reflect our experience, although we cannot comment on how much effort has been put in by Sponsors “behind the scenes”.
- Our expectations remain unchanged for future trials.
- The biggest barrier to innovation from our perspective is not seeking advice from the regulator early enough, or at all.

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