SIMBEC-ORION

About Simbec-Orion

- Full- service international Contract Research Organisation
- Headquartered in the UK with more than 450 employees across Europe and North America
- Early stage clinical development, FiH, HV & patient studies from our purpose built MHRA-accredited facility
- Late stage trials conducted in collaboration with sites across Europe, North America & beyond
- Particular expertise in oncology & rare disease programs
- Predominantly supporting small to mid-size pharma & biotech companies, both in Europe & North America, with a comprehensive portfolio of services including central laboratories, IMP Management, Pharmacovigilance & Regulatory Support

SIMBEC-ORION

Introducing your moderator & presenter

Dr Danielle Webb has over 10 years of experience in clinical research, having joined Simbec-Orion in 2013.

Danielle has a PhD from the Welsh School of Pharmacy and has previous non-clinical experience in pulmonary pharmacology and pharmacokinetic modelling. Danielle also holds a Certificate in Human Pharmacology from the Faculty of Pharmaceutical Medicine (Royal College of Physicians).

Danielle has practical experience and scientific knowledge of the design, management, analysis and reporting of clinical development projects with an emphasis on first-in-human pharmacology, and phase I pharmacology and PK studies.

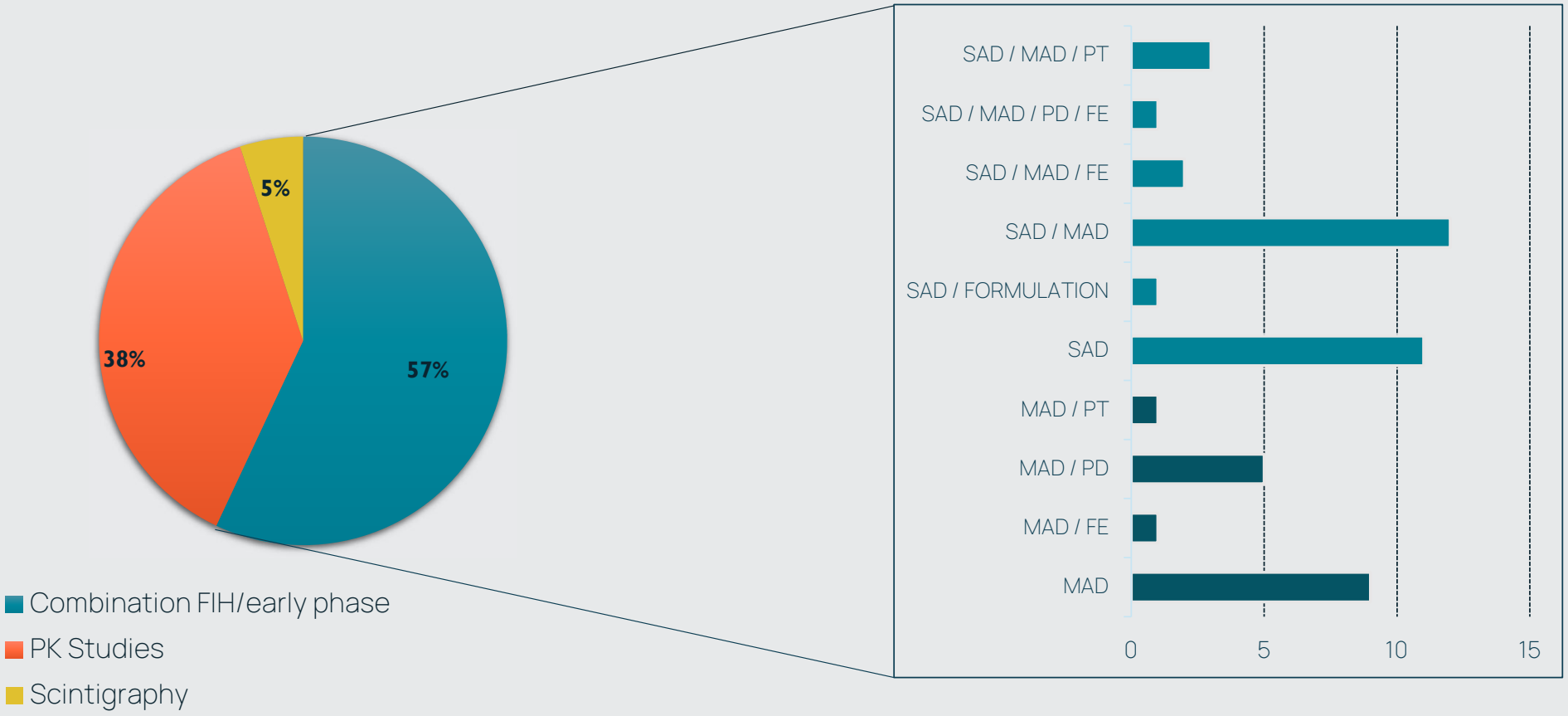
Dr Kirsty Wydenbach was recently appointed Head of Regulatory Strategy at Weatherden, a global integrated clinical consultancy. With over 13 years' experience as an Expert Medical Assessor at MHRA within the Clinical Trials Unit, Kirsty has been involved in the UK regulation of clinical trials across all therapy areas and all phases of development, including ATMPs and many first-in-man studies.

Kirsty has also been involved in European discussions aiming to establish an EU harmonised approach to clinical trials and was an EMA expert for the update of the First-in-Human guideline.

SIMBEC-ORION

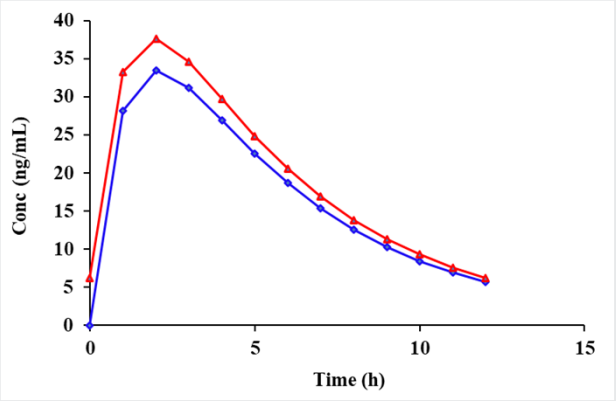
Early Phase Clinical Trials

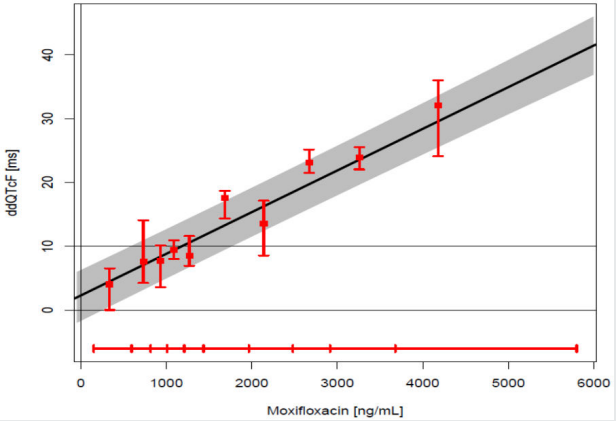
Simbec Orion Clinical Pharmacology Unit:
Recent Study Experience (prev. 10 years)



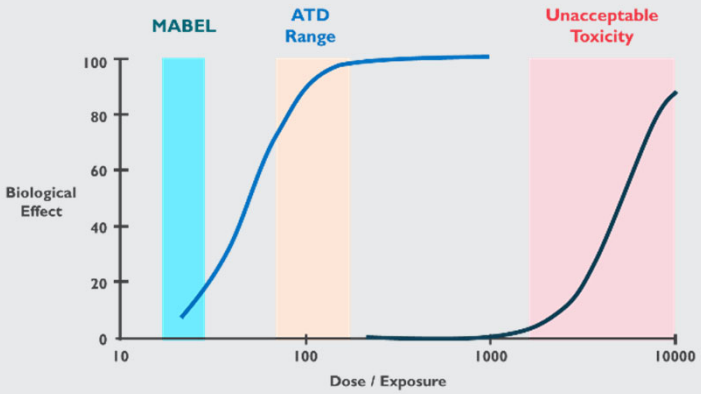
FIH & Early Phase Studies - Objectives

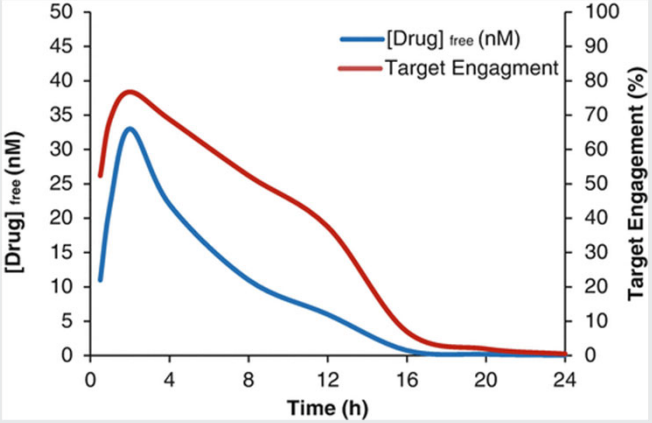
- Single Ascending Dose
- Multiple Ascending Dose
- Food-Effect
- Formulation Effect
- Drug-Drug Interaction
- Gender Effect
- Cardiac Safety
- Target Engagement
- Proof of Concept





Conc [ng/mL]





SIMBEC-ORION | Weatherden

Clinical Considerations for Early Phase Clinical Trials

Dr Kirsty Wydenbach

- Simbec-Orion Clinical Pharmacology Scientific Advisory Board
- Head of Regulatory Strategy, Weatherden

Outline

SIMBEC-ORION

- Guidance and finding information
- Top tips
- Risk – benefit
- Novel design
- Key considerations
- Population
- Dosing considerations
- Other bits and bobs
- CTA application process
- UK links to the EU
- Future updates

Guidance and sources of information

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.

Flexibility is allowed.

It is not a recipe for these trials.

Nor is it legislation – it is a scientific guideline.

If there are any issues – ASK!

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2016
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

Draft

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	<DD Month YYYY>
Date of coming into effect	<DD Month YYYY>

SIMBEC-ORION

Guidance and sources of information

1

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

- Trials characterised by extensive prospective adaptations such as planned additions of new Investigational Medicinal Products (IMPs) or new target populations.

2

MHRA website – clinical trial section

- Applications, amendments, safety

3

MHRA Clinical Trial Helpline

- 020 3080 6456
- clintrialhelpline@mhra.gov.uk

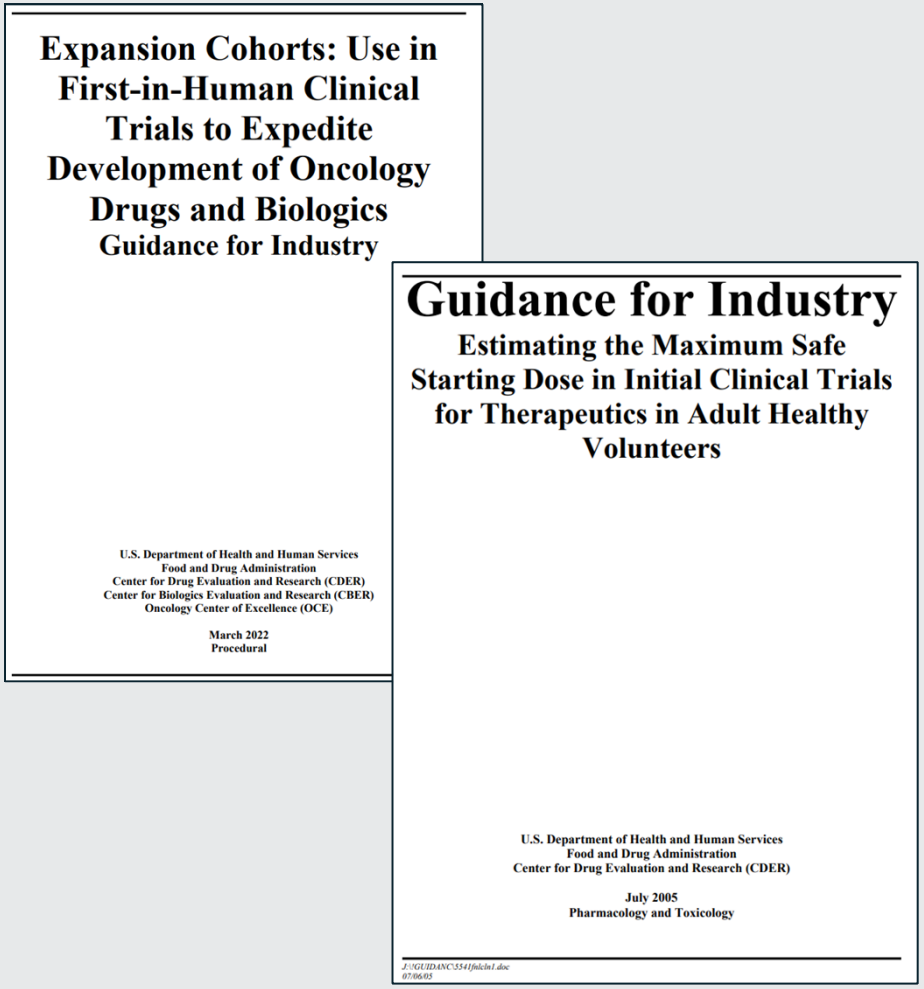
4

Advice

- Regulatory
- Scientific
- Innovation office

SIMBEC-ORION

Guidance and sources of information



- FDA guidance: trial designs that employ multiple, concurrently accruing subject cohorts, where individual cohorts assess different aspects of the safety, pharmacokinetics, and antitumor activity of the drug product.
  - e.g., paediatric or elderly subjects, subjects with organ impairment, subjects with specific tumour types
- FDA Starting dose guidance – 2005
  - Good overview of guiding principles

SIMBEC-ORION

Top tips

Make sure you review the MHRA common issues documents.

- Validation
- Non-clinical
- Clinical
- Pharmaceutical
- Useful resources

Top tips

- Be aware the rules of engagement are different for a trial review compared with a license application
  - Different assessment teams
  - CTA application review is all about safety and risk-benefit, plus ensuring the design protects the scientific integrity of the data accrued

- CTA assessment does NOT
  - Optimise protocols
  - Advise on formulation development
  - Review documents in the context of the complete clinical development plan

- Assessors are scientific but are probably not as expert as you on aspects such as mechanism of action
- Do not make assumptions – lots of justification / diagrams
- Be consistent

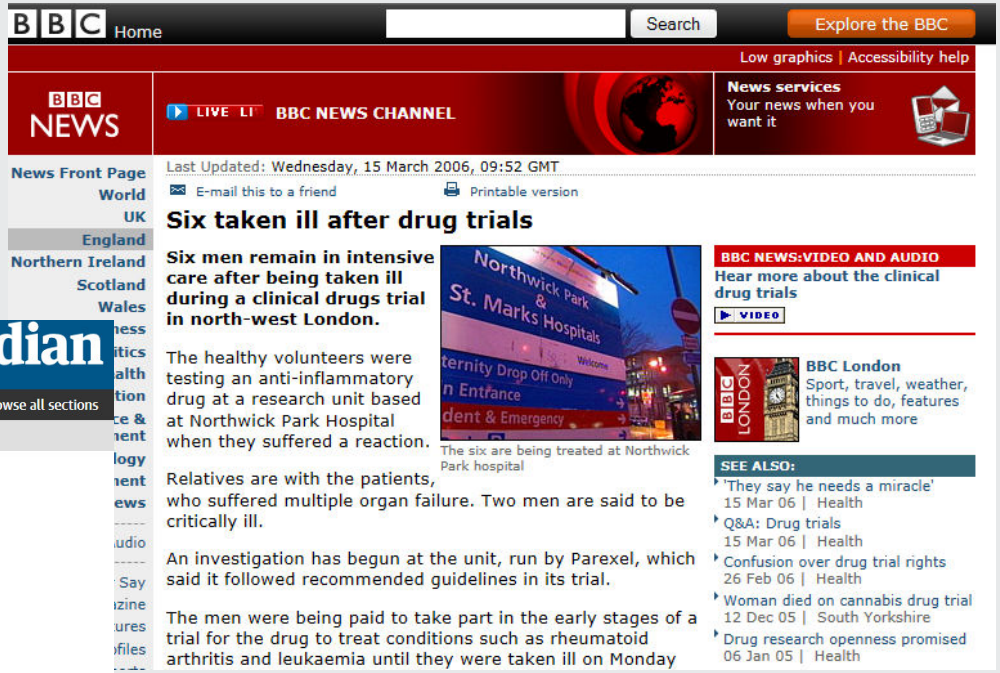
SIMBEC-ORION

The safety of FIH trials is very good…

However….

2006 - TGN 1412 (UK)

2015 - BIA 10-2474 (France)



BBC Home | Search | Explore the BBC

Low graphics | Accessibility help

BBC NEWS | LIVE LI BBC NEWS CHANNEL | News services: Your news when you want it

News Front Page | World | UK | England | Northern Ireland | Scotland | Wales

Last Updated: Wednesday, 15 March 2006, 09:52 GMT

E-mail this to a friend | Printable version

Six taken ill after drug trials

Six men remain in intensive care after being taken ill during a clinical drugs trial in north-west London.

The healthy volunteers were testing an anti-inflammatory drug at a research unit based at Northwick Park Hospital when they suffered a reaction.

Relatives are with the patients, who suffered multiple organ failure. Two men are said to be critically ill.

An investigation has begun at the unit, run by Parexel, which said it followed recommended guidelines in its trial.

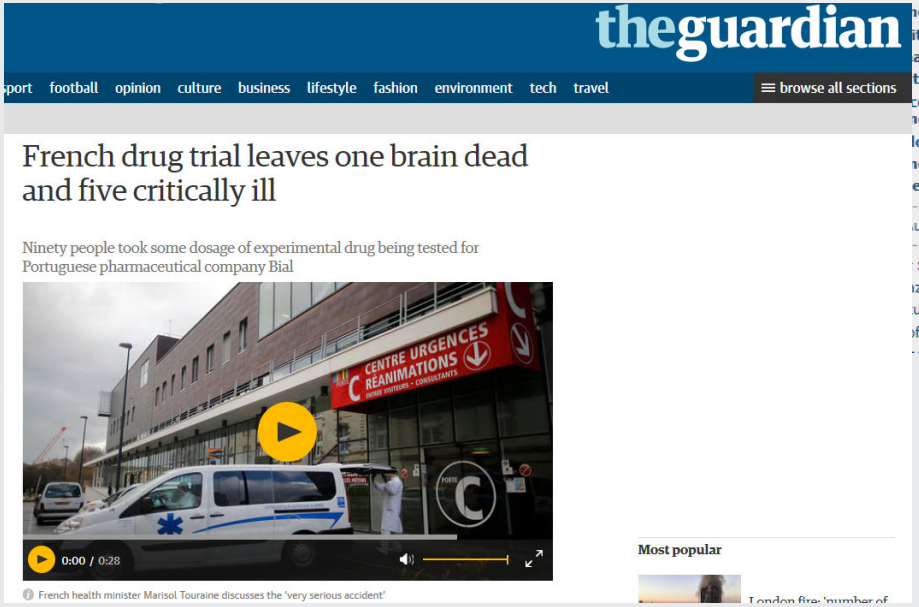
The men were being paid to take part in the early stages of a trial for the drug to treat conditions such as rheumatoid arthritis and leukaemia until they were taken ill on Monday

The six are being treated at Northwick Park hospital

BBC NEWS:VIDEO AND AUDIO
Hear more about the clinical drug trials
VIDEO

BBC London
Sport, travel, weather, things to do, features and much more

SEE ALSO:
- 'They say he needs a miracle' 15 Mar 06 | Health
- Q&A: Drug trials 15 Mar 06 | Health
- Confusion over drug trial rights 26 Feb 06 | Health
- Woman died on cannabis drug trial 12 Dec 05 | South Yorkshire
- Drug research openness promised 06 Jan 05 | Health



theguardian

sport | football | opinion | culture | business | lifestyle | fashion | environment | tech | travel | browse all sections

French drug trial leaves one brain dead and five critically ill

Ninety people took some dosage of experimental drug being tested for Portuguese pharmaceutical company Bial

French health minister Marisol Touraine discusses the 'very serious accident'

Most popular

Risk-benefit

- Decisions made based on safety considerations (Benefit vs. Risk)

'Do the data supplied support the use of this product, administered in this way, in the proposed dose for the proposed duration, to this 'type' of participant?'

- There is risk associated with all trials
- The degree of acceptable risk depends on a number of factors
- Risk: Benefit in a healthy volunteer FIH trial may be very different from a Phase 3 cancer study
- Be aware of what data is missing – what don't you know
- Constantly re-evaluate the risk-benefit

Risk-benefit

- Review what is known about the mechanism
  - Some events will almost always be drug related
    - Anaphylaxis
    - Stevens-Johnson syndrome
  - Are multiple signalling pathways involved, and how do they interact with each other
  - Is there an immunological aspect (particularly amplification)
  - Is there a cascade mechanism involved (such as coagulation)
  - What cytokines are involved (increase / decrease)

For every aspect consider:
- What can be monitored?
- What non-clinical signals are reversible, or not?
- Are biomarkers or surrogate endpoints possible to monitor?

SIMBEC-ORION

Key considerations

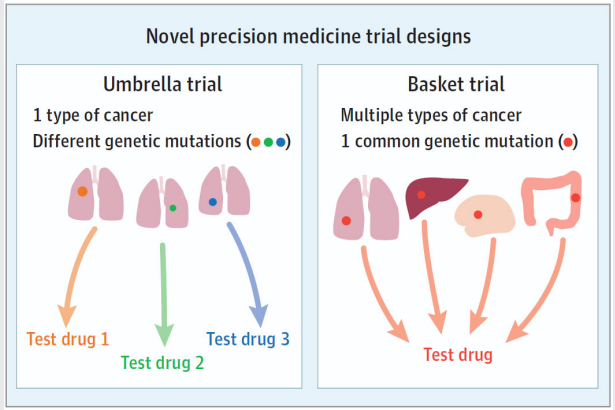
- Keep asking 'why'
  - Why have we seen raised liver enzymes
  - Why is the PK profile not as we predicted
- Sentinel dosing
  - Why do we need it?
- Stopping rules
  - Flexibility is acceptable but what will make you stop (what data, in how many, over what period)
    - Individual
    - After sentinel subject
    - Cohort
    - Dose escalation
    - Previous dose levels / cohorts
    - Whole study

Novel designs

- Consider what is needed to balance risk-benefit and participant safety, but also balance obtaining data with being efficient.

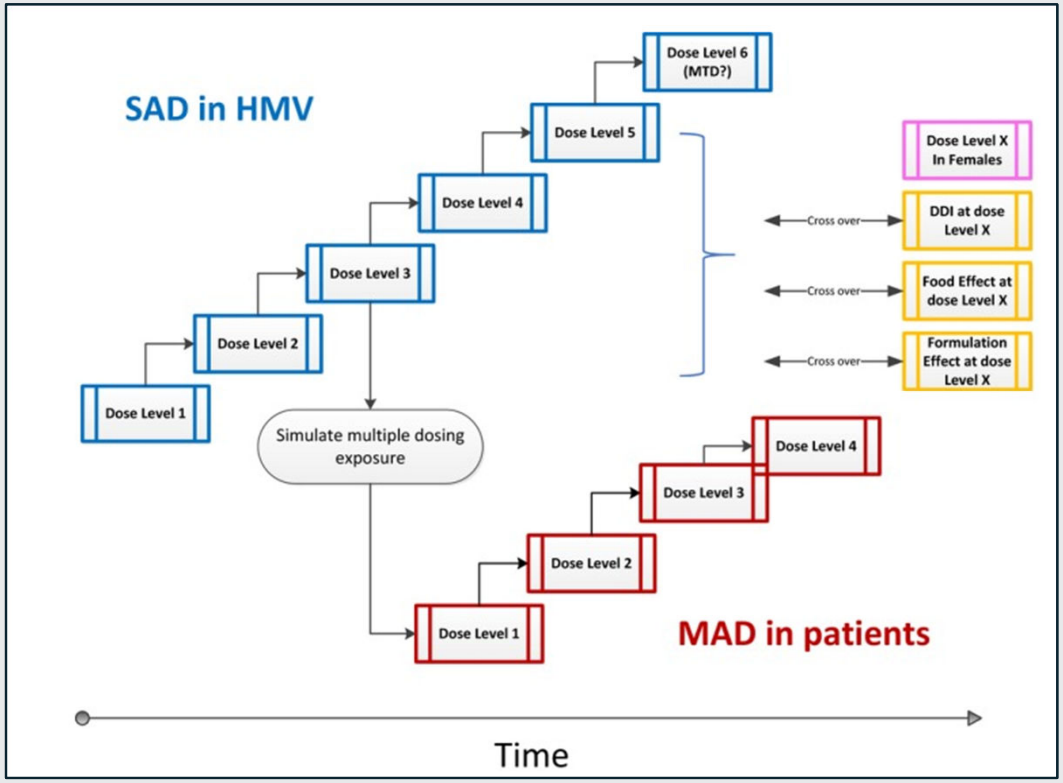
- A good example is COV001 – the FIH trial for the AZ vaccine [protocol]
  - Proposed the objectives and endpoints, worked out the schedule they needed to work to, discussed it with MHRA and worked on how to balance the risks (FIH vaccine, known platform technology) with the benefits (COVID vaccine)
  - Multiple overlapping groups, sentinel dosing in some parts, amendments to add cohorts for safety (pre-dose paracetamol)
  - Clear safety reviews, clear dosing decisions and justifications

- Novel designs (aka complex innovative designs) can be used.
  - British Journal of Cancer https://doi.org/10.1038/s41416-019-0653-9



Novel designs

- After dose escalation +/- expansion cohorts, what else can we learn in this FIH trial?
- Consider:
  - Other populations
    - Different age groups
    - Obese
    - HV / patient
  - Drug interaction
  - Challenge agents
  - Food effect
  - Different formulations
  - Early phase 2 elements



SIMBEC-ORION

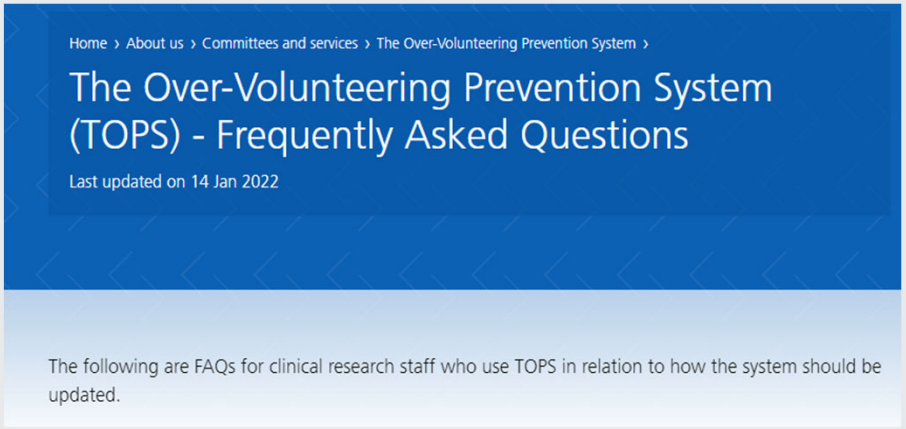
FIH population

- Healthy volunteer vs patient

- Consider:
  - Severity of toxicity and safety events seen in animals
  - Reversibility of events
  - Can events be monitored and treated
  - Off-target effects?
  - Is the target expressed in HVs?

- Healthy volunteer
  - Eligibility criteria usually very strict

- Consider including both!
  - Switch mid dose escalation / different cohorts



SIMBEC-ORION

Clinical dosing considerations

Starting dose

- At what point is pharmacological activity expected
  - HV – start below this with a justified safety margin
  - Patients – expect to start at a pharmacologically active dose or get to that level quickly, unless non-clinical safety warrants a more cautious approach

Intermediate doses

- Dose increments between the defined starting and top doses

Top dose

- How high do you actually need to go?
  - Especially in healthy volunteers >2-3x above the top of a predicted clinical range needs robust justification.
  - Consideration for several potential future clinical programmes is acceptable, but justification should still be on safety grounds – higher doses can always be evaluated later in patients
- Do you have a safety margin?

Be as transparent as possible on the justification, for all aspects, including regimen and route of administration.

SIMBEC-ORION

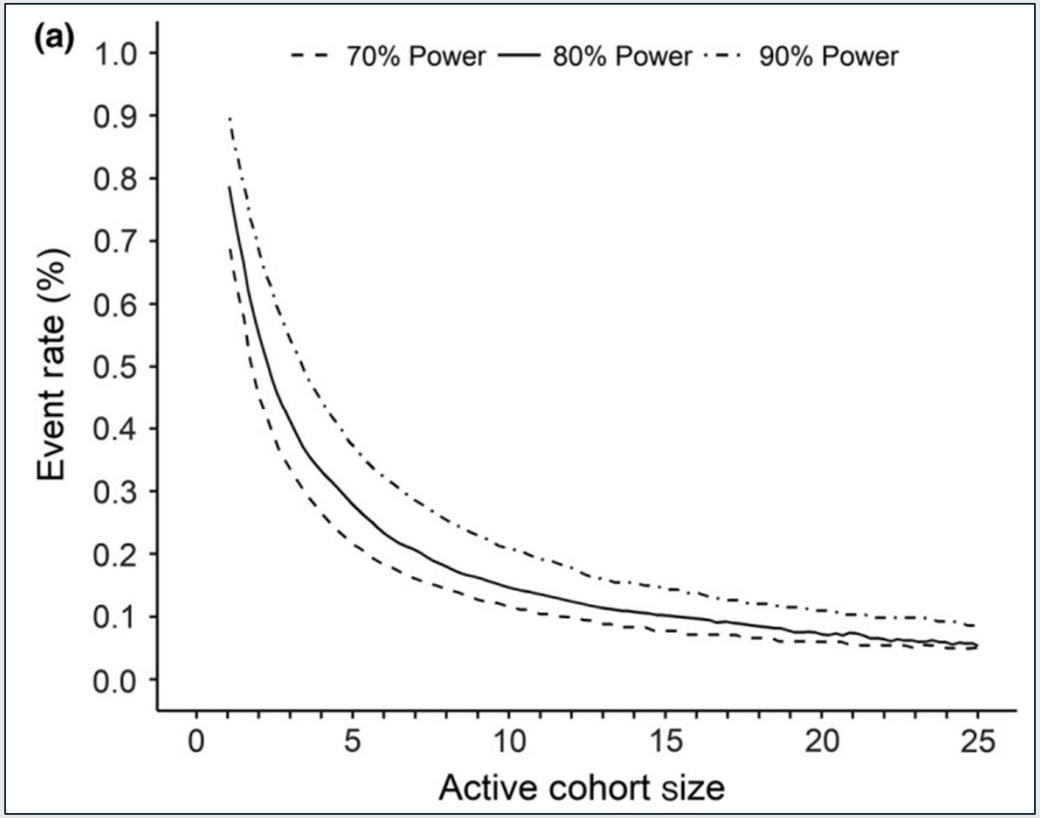
Dose escalation decisions

- Amount of data reviewed needs to be clear in the protocol
  - Number of subjects – active and placebo
  - Amount of data – what data / how many days
    - Safety / PD / PK
  - Cumulative reviews encouraged (rolling review of emerging data)

- Reviewing PK data for dose escalation is often overlooked
  - Complex assays could be a reason not to review PK
  - Data can feed back into models and update them quickly
  - Consider LLQ
  - Its also about setting the starting dose correctly

Other bits and bobs

- Cohort sizes
  - Why 6+2?
- Blinding – placebo or no placebo?
- CTCAE – not considered appropriate for HVs



CTA Application processes

SIMBEC-ORION

- Now Combined Review with the Ethics Committee
- All FIH trials are peer reviewed through a discussion meeting once a week, with all CT assessors
- Higher risk First in Human studies also receive external independent expert advice
  - Expert Advisory Group and Commission on Human medicines (CHM)
- Assessors do not specialise – everyone does everything

UK links to the EU

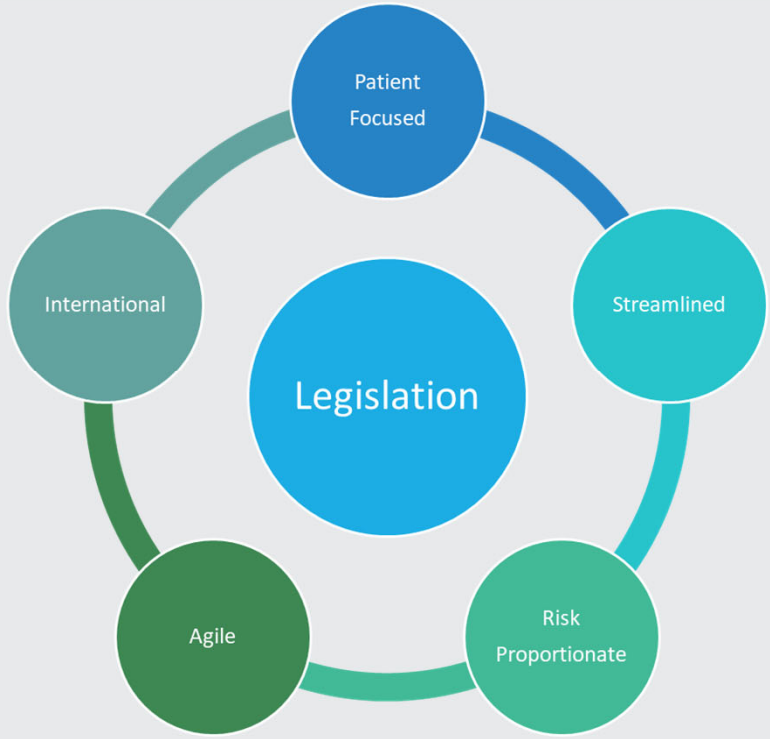
- Clinical Trials Regulation (CTR) [EU Reg 536/2014] came into force in 2014 and was applicable from 31st January 2022.

- UK is no longer in EU so is not implementing the CTR, although aims to align where possible
  - The CTR will not take effect in Northern Ireland – this remains under the remit of MHRA as part of 'UK' regulation

- There is a 3 year transition period – CT Directive will not be used for new CTA applications after January 2023

- There is extensive training and support online, as well as a modular training programme and many Q&A documents for each element of a new CTA and maintaining a CTA

Future UK updates



SIMBEC-ORION | Weatherden

Thank you!

For more information, or to submit an RFP

SIMBEC-ORION

www.simbecorion.com

information@simbecorion.com

https://www.linkedin.com/company/simbecorion/