Update on regulatory considerations for early clinical development (including Brexit) – Industry perspective

EUFEMED 2019 Conference

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What I will Cover

- Impact of Brexit on clinical trials
- Revision of the EU First in Human Guidance
- Clinical Trials Regulation
- Look to the Future and Different Types of Trials

Pre-Brexit related changes for clinical trials

	Nature of Brexit change	Amendment type (Pfizer view)
Labelling and packaging site	Add **EU-27 sites** as additional sites	(Substantial)
QP release site	Add **EU-27 site** as an additional site	(Non-substantial)
Legal representative	Replace UK-based LR with **EU-27-based LR**	(Non-substantial) But considered substantial by some MS

Total # submissions

~650 submissions covering 107 protocols across 26 EU/EEA markets

Post-Brexit Concerns for Clinical Trials

Cause for concern is limited:

- MHRA guidance pragmatic
- CT market is ‘national’ so national CTAs and approvals (based upon existing requirements)
- Trials (UK-included) conducted to international standards, thus data from UK trials applicable post-Brexit as it is pre-Brexit

Key issues:

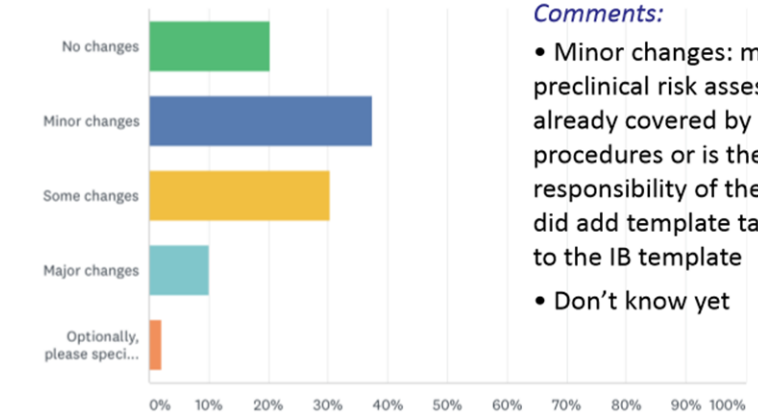
- Border delays
  - Getting IMPs and APIs across the EU/UK border seamlessly
- Duplication of activities in the UK:
  - QP certification with UK-based QPs
  - Safety reporting

EU First in Human Guidance: Impact on EU Research

Specific questions

To what extent will the implementation of the revised nonclinical requirements impact on your current practices?

Beantwortet: 99 Übersprungen: 26



Comments:

- Minor changes: most of the preclinical risk assessment was already covered by existing procedures or is the responsibility of the sponsor. We did add template tabular formats to the IB template
- Don't know yet

Specific questions

Overall, what level of change do you expect in your current practices for FIH and early phase trials with the implementation of the revised guideline?

ANTWORTOPTIONEN		BEANTWORTUNGEN	
No effect		9.28%	9
Minor changes		41.24%	40
Some changes		38.14%	37
Major changes		7.22%	7
Optionally, please specify the key changes:	Responses	4.12%	4

Results from a Survey Presented at EUFEMED 1st Forum on 'Revised FIH EMA Guideline: Disruptive or Constructive?', 19-Sep-2018

EU First in Human Guidance: Impact on EU Research

Impact on European Union / Innovation

Overall, what impact will the implementation of the revised guideline have on the European Union?

ANTWORTOPTIONEN		BEANTWORTUNGEN	
Very negative		2.06%	2
Rather negative		11.34%	11
Neutral		45.36%	44
Rather positive		29.90%	29
Very positive		5.15%	5
Optionally, please specify:	Responses	6.19%	6

- This will depend more on the timelines of the new portal and submission process than on the revised guideline.
- It will increase the burden of doing FIH trials, but enhance the safety for the subjects
- Depending on the interpretations by the competent authorities
- Can't say
- The problem it tries to resolve (off target activity) is untouched
- That guideline is badly written, the contents are not clear, there's a mix of several study types, and the fact that advertising for umbrella protocols is made is really disadvantageous. Overall, the impact of that guideline is very negative

Impact on European Union / Innovation

Overall, do you think that the implementation of the revised guideline could have consequences on innovation?

ANTWORTOPTIONEN		BEANTWORTUNGEN	
Yes		40.00%	38
No		60.00%	57
Optionally, please specify:	Responses	0.00%	0
TOTAL			95

Impact on European Union / Innovation

Overall, do you think that the implementation of the revised guideline could have consequences on innovation? YES:

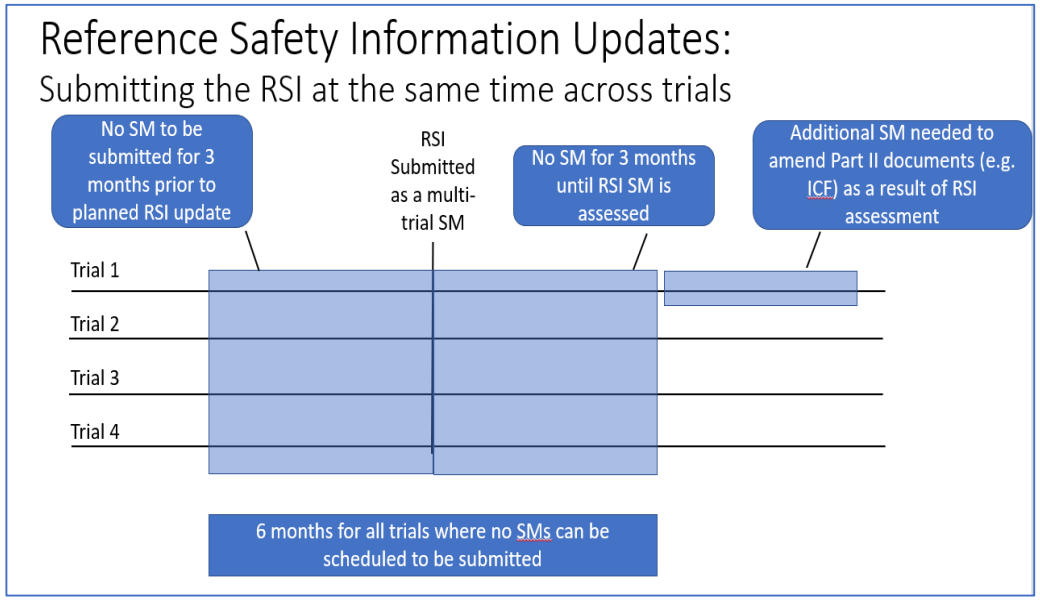
ANTWORTOPTIONEN		BEANTWORTUNGEN	
Very negative		5.00%	2
Rather negative		42.50%	17
Neutral		15.00%	6
Rather positive		32.50%	13
Very positive		0.00%	0
Optionally, please specify:	Responses	5.00%	2

Overall Conclusion:

Survey suggests the revised guidance is not overwhelmingly negative but should question whether it is too early to identify the impact of the revised guideline EU clinical trials. Active collaboration and communication are needed for effective translational science, and to maintain research in Europe.

Clinical Trials Regulation: A Different Way of Working

- Same rules apply for early-phase studies as they do for later-phase studies – limited options for adaptation
  - Documentation in CTAs
  - Use of complex EU Portal & Database
  - Approval timelines – as slow as the slowest MS
- Substantial modifications – a potential challenge
  - Submitting a SM prevents the ability to submit another SM until the first SM assessment is completed (could take up to 94 days)
  - Rejection of one SM in a grouped SM submission leads to a rejection of all SMs in the group
    - Sponsors' reluctance to group too many SMs
- Still requiring consideration: Interaction between the CTReg and other EU legislation (GDPR, Medical Derive Regulation)



Data Disclosure from EU Database

Generally satisfied that:

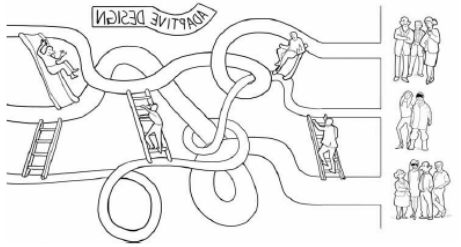
- Disclosure of most sensitive data can be deferred:
  - Options to protect disclosure of phase I data and results
  - IMP CMC data is protected
  - Process for disclosure is automated

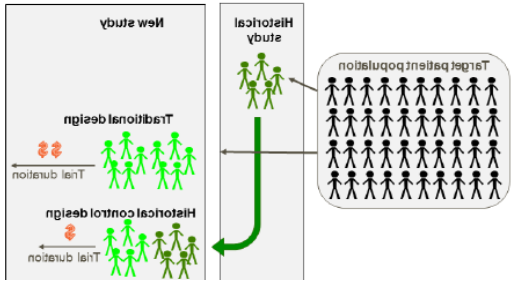
Outstanding concerns:

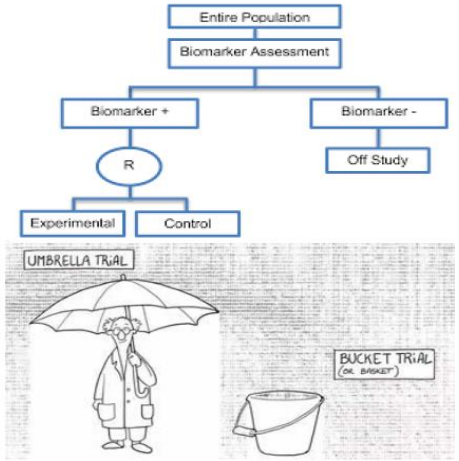
- Lingering ex-EU concerns that data from early-phase trials is not sufficiently protected
- Assessment reports and LoQ could be disclosed even if disclosure of protocol/IB is deferred
- Process for redaction of CMC-related questions/comments in ARs and LoQ
- Not able to extend deferral timelines once selected
  - Maximum timelines for deferral will always be selected

In the Future there will be Many Different Trial Designs to Choose From…

- Enhanced Use of RWE in Clinical Trials
  - RWE for indirect comparisons
- Model Informed Drug Development
  - Modelling, simulation & extrapolation,
- Complex Innovative Trial Designs
  - Adaptive statistics,
  - Umbrella & Basket studies
  - Platform studies with Master protocols,
  - Historical controls
- Biomarker validation







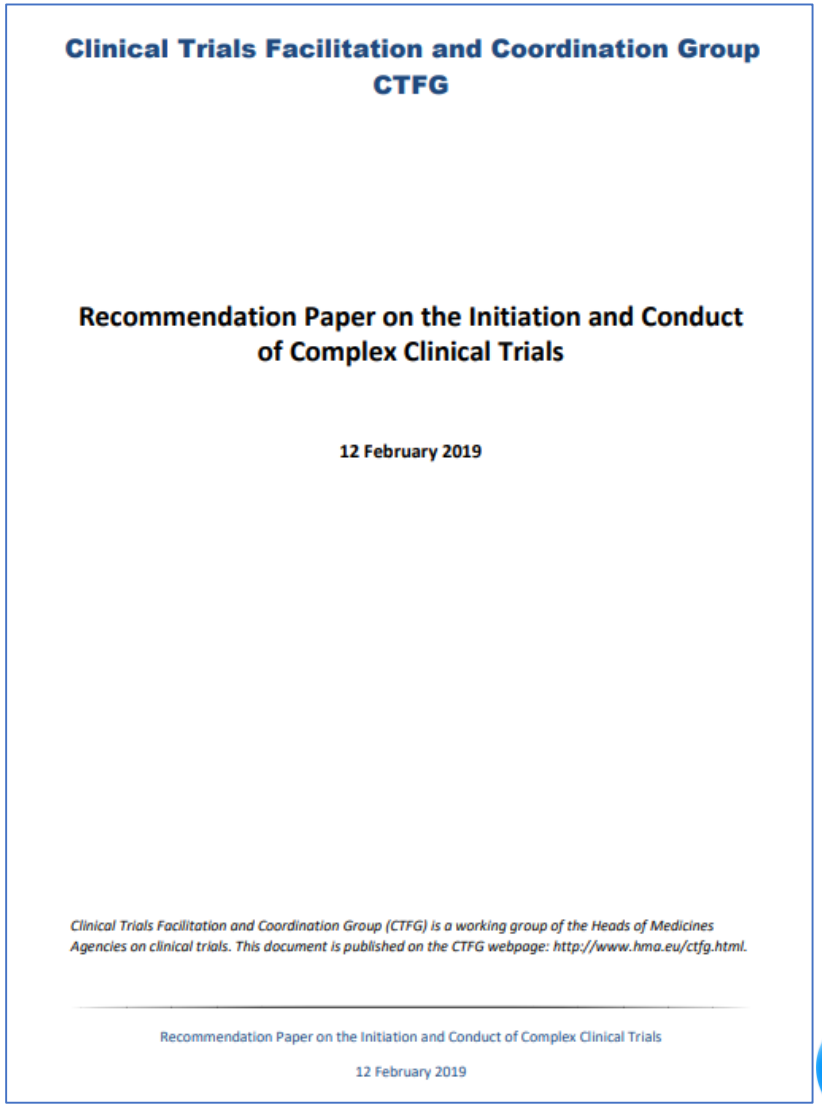
….in addition to the standard RCT

Will These Trials Impact Early Clinical Research?

"Complex clinical trials are most often early exploratory trials where a limited amount of safety and efficacy data of the IMP(s) being tested is available"

"A clinical trial is a clinical investigation with a pre-defined objective aimed at addressing a precise hypothesis"

- EFPIA has questioned the accuracy of these statements



Clinical Trials Facilitation and Coordination Group
CTFG

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

12 February 2019

Clinical Trials Facilitation and Coordination Group (CTFG) is a working group of the Heads of Medicines Agencies on clinical trials. This document is published on the CTFG webpage: http://www.hma.eu/ctfg.html.

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

12 February 2019

In Summary

- Some significant headwinds for conducting early clinical research in the EU:
  - Brexit (Short-term)
  - Revised FIH Guidance – Challenge and/or opportunity
  - CT Regulation (Timeline to be determined, interaction with other legislation)
  - Different trial designs

- If we continue to be innovative, tenacious and committed to patients, we will overcome these