News from Brussels and London regarding EU Regulation 536/2014

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Col – Statement and Caveat

• There are no conflict of interests to declare.
• The views expressed here do not necessarily represent exactly those of AKEK Germany.
The CTR 536/2014 requires that many existing guidelines have to be updated and many new ones have to be written and consented, e.g.

- Ethical Considerations on clinical trials with minors
- Note for Guidance re lay summary of results of a clinical trial
- Note for Guidance re emergency trials
- Paper for transitional period
- Note for Guidance re informed consent
“Informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial and that all of the following conditions are fulfilled.”
Clinical Trials in Emergency Situations: Article 35 (1.)
CTR 536/2014

a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial

b) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition

c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;
d) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial *previously expressed* by the subject;

e) the clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations;

f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in *comparison with the standard treatment of the subject's condition*;
Where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the subject as soon as he or she is capable of giving informed consent.

If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical trial. (3.)
Problems (35.1.)

➢ Emergency situations – Definition?
➢ Restriction to include subjects with known identity only? When the investigator judges that the likelihood of obtaining later consent after the first trial specific intervention is high?
➢ Efforts to secure ”no prior objections by potential subject” in case of an emergency? How to ?
➢ ”Direct clinically relevant benefit”, use of surrogate endpoints permitted ?
➢ Special considerations on design, endpoint, placebo-control;
Problems (35.1.)

- Minimal R&B in comparison with the standard treatment of the subject's condition. What does that mean?
- Non-inferiority trials permitted?
Problems (35.2.)

- Time windows when informed consent should be sought after the first intervention - ”without undue delay” - Definition
- Use of data if subject does not give consent or dies?
Aspects

✓ Placebo Control should be permitted at least when standard treatment is not evidence-based, and as add-on to standard treatment.
✓ Surrogate endpoints should be permitted if properly validated.
✓ Trials / interventions with chance for group-benefit are not permitted.
There are a lot of activities and much more transparency, but paper doesn’t blush.

Given that EMA has to move to AMS and that the promised building in AMS seems to be not available / ready in time, I suspect the EU Portal & DB will not be ready before 2020.
### ‘Traffic lights’ - Status October 2017

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*August, **May, ***March information assumed still to be valid

- Little progress, major hurdles remain,
- Some progress, more activity needed,
- Progressing well, on target

Overall national reorganisation is about 50% on track

Areas of least progress: Safety, resources and national IT
Traffic lights’ - Status October 2017: Results

Major Problems seen in three areas:

- Resources
- National IT System
- Safety
CTFG - ‘MS Readiness’

• Traffic light table prior CTFG plenary 24/25\textsuperscript{th} October:
  A few never respond, some seldom….

• National re-organisation about 50\% on track:
  – NCA/EC: only 1 MS with major hurdles
  – EC: overall 46\% on track, while the ones with reorganization 30\%
  – National law: 43\% on track, and 3 MS with major hurdles (11\%)

• Pilot projects:
  – 19 MS want to test and thereof 53\% on track
  – 9 MS not plan any
MS Readiness

• Fee: approx. 60% still orange

• Communication and training:
  – Only 21% on track
  – 57% orange
MS Readiness – Major hurdles

National IT system highly depends on functionality of EUPD and interface to national systems

- Overall 1/3 of MS on track, 2/3 of MS have hurdles
- Within MS who need national IT system:
  - >85% of MS with hurdles!
  - 9 of 22 MS with major hurdles

Resources only 6 MS (21%) are on track yet, while 9 MS have major hurdles
Safety - The least readiness

• Safety
  – 19 MS (46%) have major hurdles
  – Only 6 MS (21%) are on track

• CTFG Annual Safety Report (ASR) work sharing
  – 10 NCA/MS participate in work share process (31%)
  – 124 ASRs assessed since June 2015
    • Issues to supervise further about 27% of ASR (‘flagged’)
    • Issues with Reference Safety Information about 24% of ASR
  – Discrepancy to expected workload of >1500 multinational ASR/year
Safety – ASR work sharing

What are the hurdles?
How to solve?

• Reasons that hinder to participating - Reasons that hinder sharing of national assessment?

• Training workshops
• Twin (assess together) with an experienced NCA
• Pick IMPs you want and join anytime: ASR-WS@sukl.cz

Safety surveillance is our responsibility!