Applying CAST to the TGN1412 First-In-Human Clinical Trial: *Preliminary Results*

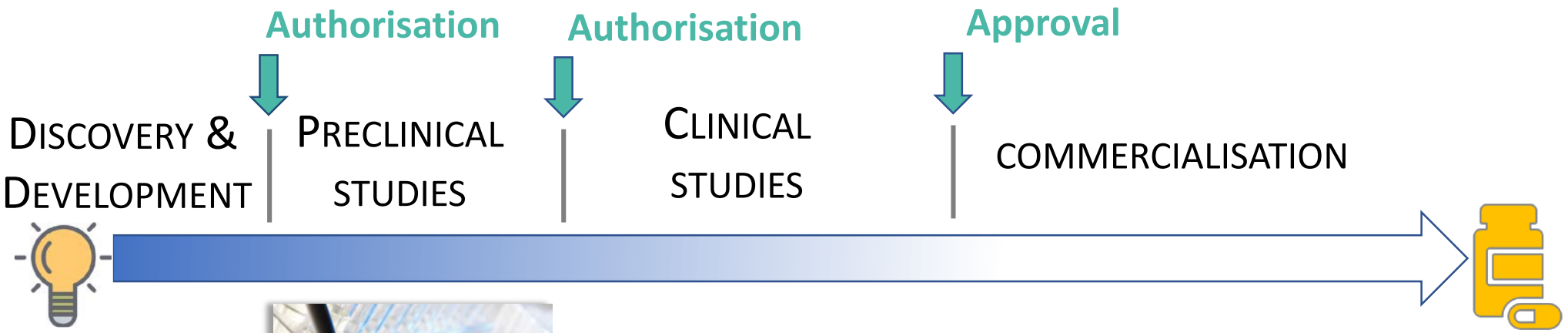
Anthony Vacher[1], Myra Daridan[2], Monica Pollina[3], Francesco Salvo[4], Simon Whiteley[5] Brian Edwards[6], for the Safety Analysis Team

[1] *Armed Forces Biomedical Research Institute, France*
[2] *Clinical Research Consultants, France & European Forum for Good Clinical Practice, Belgium*
[3] *Pharmacoepidemiologist, France*
[4] *Population Health Research Centre, Team Pharmacoepidemiology, Bordeaux University, France*
[5] *Whiteley Aerospace Safety Engineering & Management Limited, United Kingdom*
[6] *NDA Regulatory Science Ltd & Alliance for Clinical Research Excellence & Safety, United Kingdom*

1st November 2018
6th European STAMP Workshop & Conference, Amsterdam

How new safe and effective drugs are developed?

A highly regulated and rigorous evaluation process



In vitro models

Animal models

PHASE I: Is the treatment safe?

PHASE II: Does the treatment work?

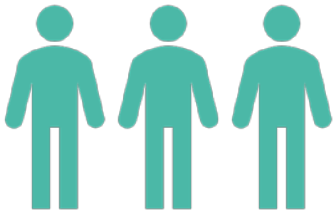
PHASE III: Is it better than what's already available?

PHASE IV:
Pharmacovigilance
Studies after approval

Safety during early phases of clinical trial involving healthcare products

A high level of safety for participants

- "Phase I non-oncological studies trials **do cause mild and moderate harms but pose low risks of severe harm.**" Johnson, et al., *Clin Trials.* 2016



- **Serious adverse events:** from 0.04% to 0.31% **"without any life threatening events or deaths"**
  Patat, et al., *ASCPT. 2011;* Emmanuel, et al., *BMJ.* 2016

Safety during early phases of clinical trial involving healthcare products

CURRENT CONTROVERSY 3

The hexamethonium asthma study and the death of a normal volunteer in research

J Savulescu, M Spriggs

Death of a normal volunteer highlights problems with research review and protection of subjects

Savulescu & Spriggs, J Med Ethics. 2002

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Suntharalingam, et al., NEJM, 2006

Minutes of the Temporary Specialist Scientific Committee (TSSC) meeting on "FAAH *(Fatty Acid Amide Hydrolase)* Inhibitors" of 15 February 2016.

French National Agency for Medicines and Health Products Safety, March 2016

What organization has been set up to learn from these accidents?

- **No independent investigation solely dedicated to safety**
- Investigations currently **focus on the healthcare product** and use **classical linear accident causation models**
- Investigations often failed to take into account from **the contribution to the many stakeholders and the interactions among these stakeholders**

CAST analysis of the TGN1412 First-In-Human Clinical Trial

Data sources

- Official summary report from the Medicines and Healthcare products Regulator Agency MHRA, 2006
- Final report of the expert scientific Group on phase one clinical trials The Duff Report, 2006

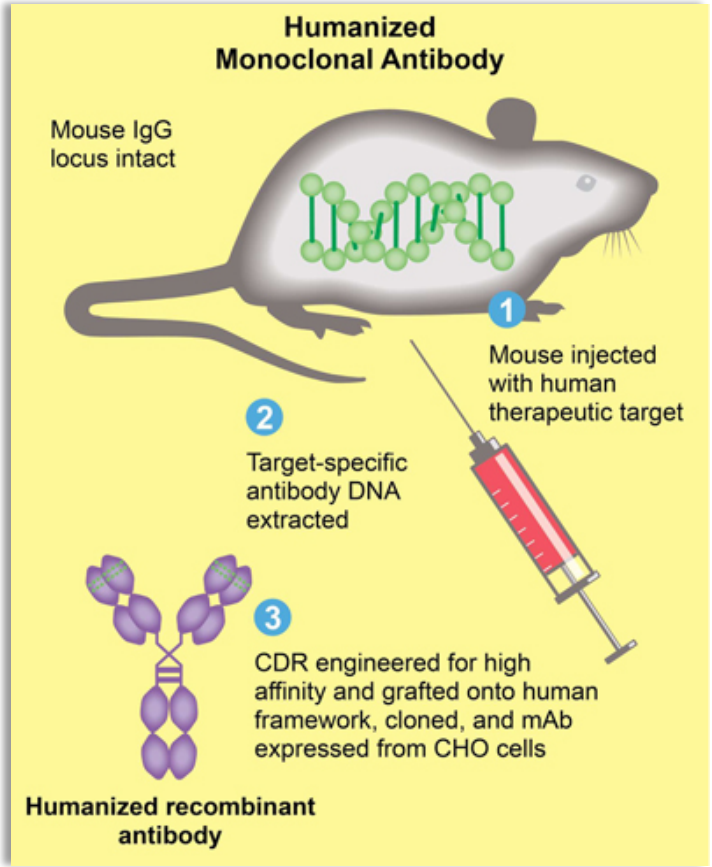
Event summary – Proximate events

First-in-human study – 13/03/2006 – Clinical Pharmacolgy Research Unit (Parexel®), Northwick Park Hospital (UK)

- Establish the safety and tolerability of a new humanized monoclonal antibody: **"TGN1412"**
- Drug development and preclinical studies: **TeGenero AG** (Sponsor)
- Conduct of the trial delegated to **Parexel®** (Contract Research Organization)
- Intravenous administration of one dose of the product to first cohort of volunteers by **INVESTIGATOR**, 10 minutes apart, between 8 and 9am
- Volunteers monitoring by investigators (as defined by protocol)

The rationale behind the development of the TGN1412

- **A recombinant humanised monoclonal antibody** that **activate resting T-cells**
- Developed as **a therapeutic agent for various life-threatening** (autoimmune diseases, leukaemia, etc.)
- **Effective in animals models** (rat, monkey, and in vitro human cells) **and in ex-vivo experiments** (blood samples from patients)



From JCAD, 2016

Immunotherapy:
an effective and promising drug class

The Nobel Prize
@NobelPrize
Follow

Just in! Nobel Laureate Tasuku Honjo, surrounded by his team at Kyoto University, immediately after hearing the news that he had been awarded the 2018 #NobelPrize in Physiology or Medicine.

2:46 AM - 1 Oct 2018

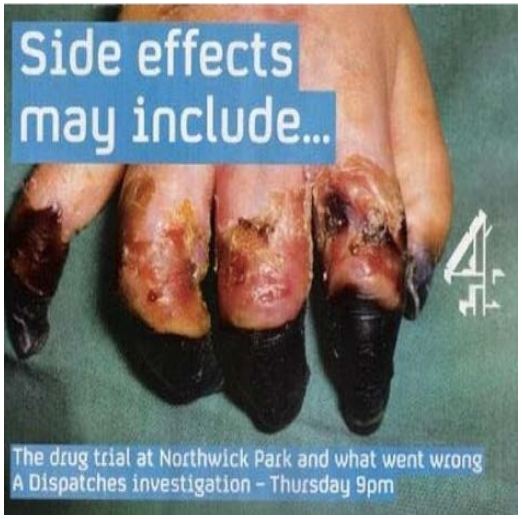
The Nobel Prize
@NobelPrize
Follow

Cheers! Friends and family celebrate James P. Allison's #NobelPrize with champagne in a New York hotel after hearing the public announcement.

5:19 AM - 1 Oct 2018

Proximate events and Losses

- First symptoms: **about one hour after the administration**
- Emergency care provided by investigators, transfer to hospital ICU between 12 and 16 hours after infusion
- **Severe and life-threating adverse reactions with multi-organ failures**
- All six volunteers survived, with **permanent sequelae** for several of them
- **Sponsor bankruptcy** due to financial and reputation losses



Firm involved in drug trial fiasco delares bankruptcy

TeGenero, the German biotechnology firm whose experimental drug TGN1412 caused multiple organ failure in six men during a clinical trial in England, has filed for bankruptcy.

Dyer, O.
BMJ, 2006

(Main) conclusions of MHRA report

- ⇒ Preclinical studies **comply with good laboratory practices**
- ⇒ **No errors** in the manufacture, formulation, dilution or administration of the drug to trial participants
- ⇒ **None of the gaps from good clinical practices** seems to have contributed to the Serious Adverse Events

"an unpredicted biological action of the drug in humans is the most likely cause of the adverse reactions"

"a relatively new type of biological drug (…) the resulting activity seen in humans was not predicted from apparently adequate pre-clinical testing (…) a complex scientific issue to be addressed"

MHRA report, 2006

System-Level Hazards and related Safety Constraints during phase I First-In-Human studies

System-Level Hazard #1

Exposure of participants (healthy volunteers or patients) to a toxic drug

Safety Constraints

SC-1.1: Participants must **not be exposed to potentially harmful drug**

SC-1.2: Means must be available, effective, and used to **minimize the consequences for participants**, if they are exposed to a harmful drug

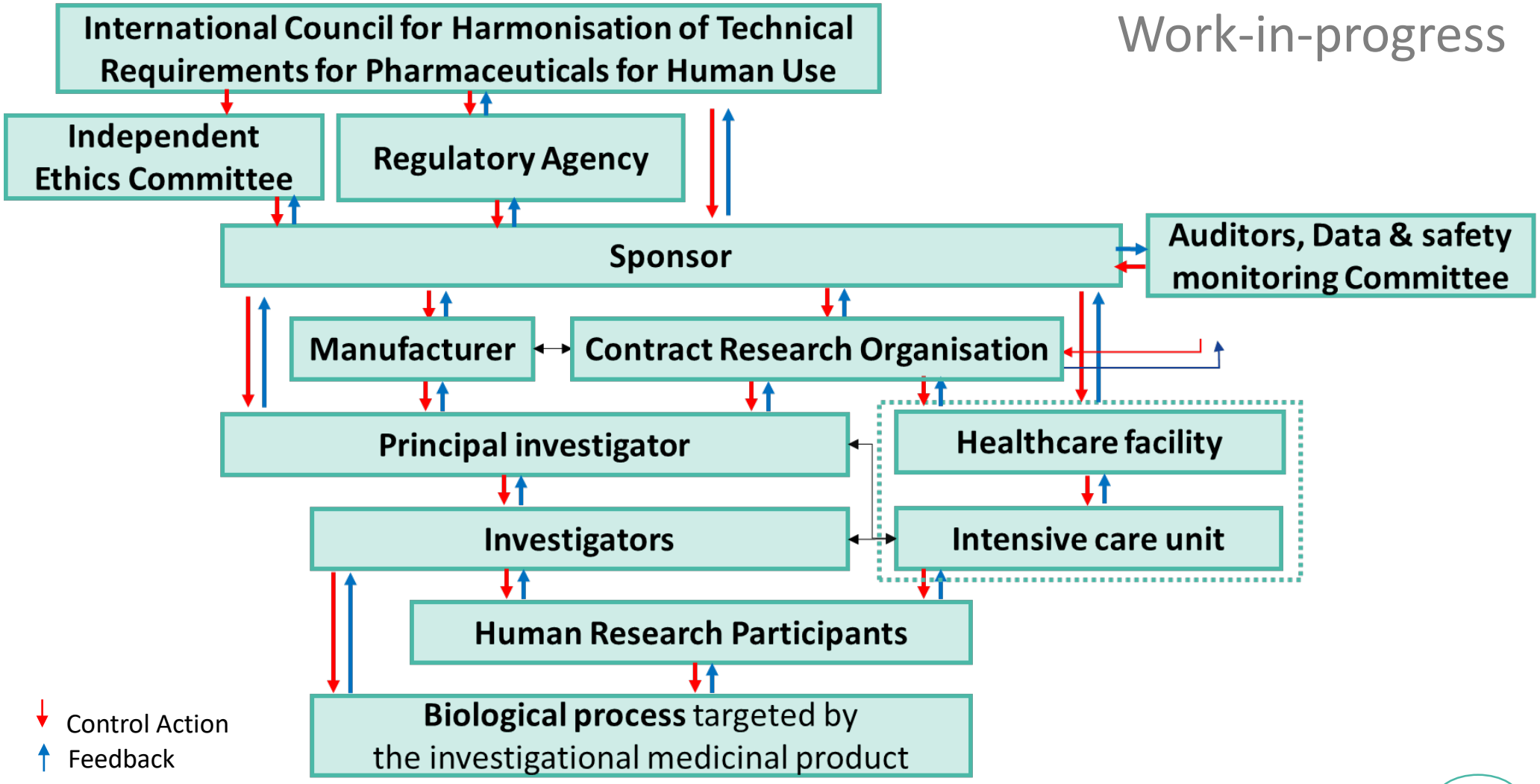
System-Level Hazard #2

Do not provide patients with an effective drug by concluding that an effective one is ineffective

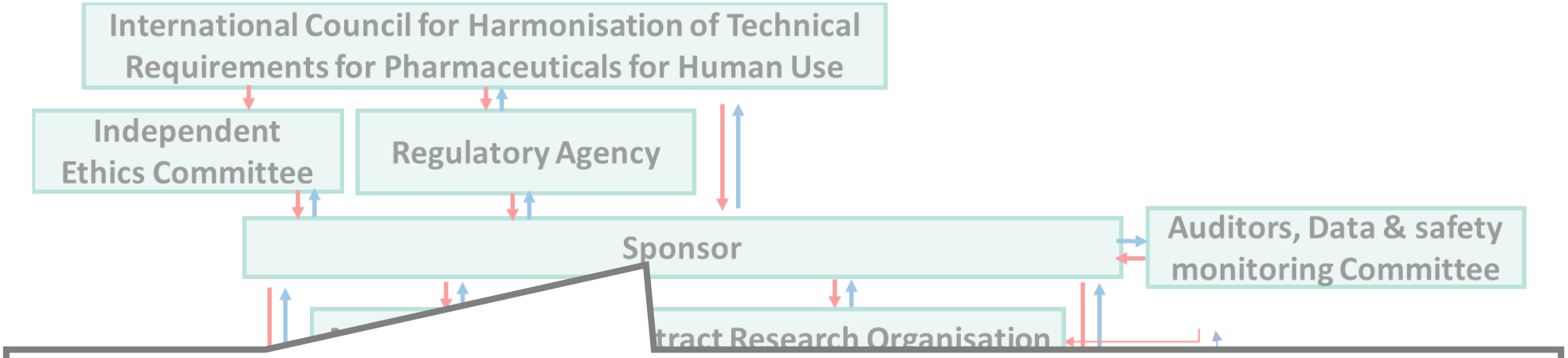
Safety Constraints

SC-2: Participants must **be exposed to a dose of drug corresponding to the one where potential biological effects in humans are observed**

The Safety Control Structure at a high level of abstraction



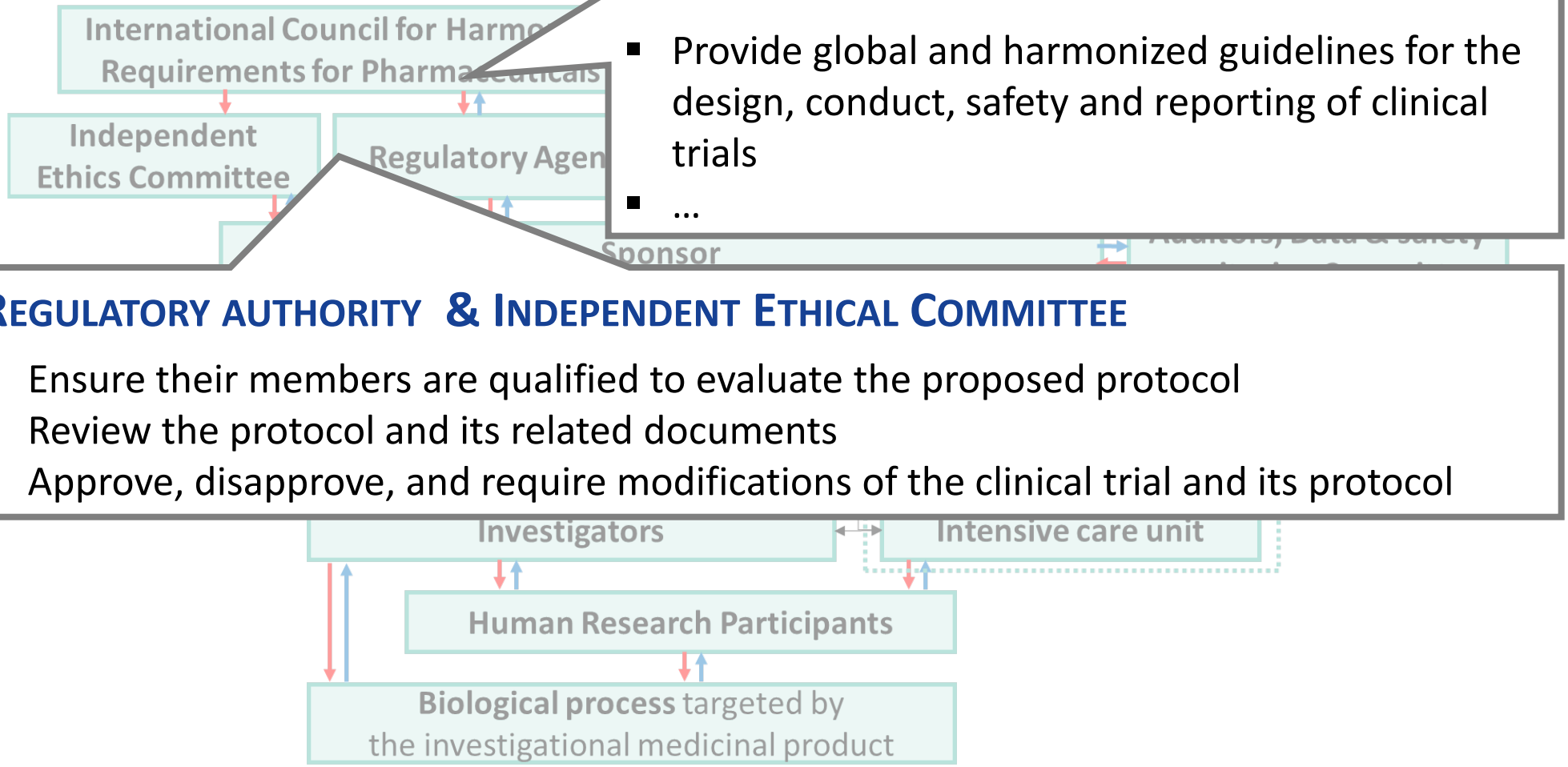
The Safety Control Structure at a high level of abstraction



SPONSOR (CONTROL ACTIONS)

- Conduct relevant preclinical studies
- Design and write the protocol (starting dose, dose escalation and timing, number of participants)
- Organize the delegation of tasks to the CRO
- Comply with clinical guidelines, ethical and regulatory requirements
- …

The Safety Control Structure at a high level of abstraction



INTERNATIONAL COUNCIL FOR HARMONISATION

- Provide global and harmonized guidelines for the design, conduct, safety and reporting of clinical trials
- …

REGULATORY AUTHORITY & INDEPENDENT ETHICAL COMMITTEE

- Ensure their members are qualified to evaluate the proposed protocol
- Review the protocol and its related documents
- Approve, disapprove, and require modifications of the clinical trial and its protocol

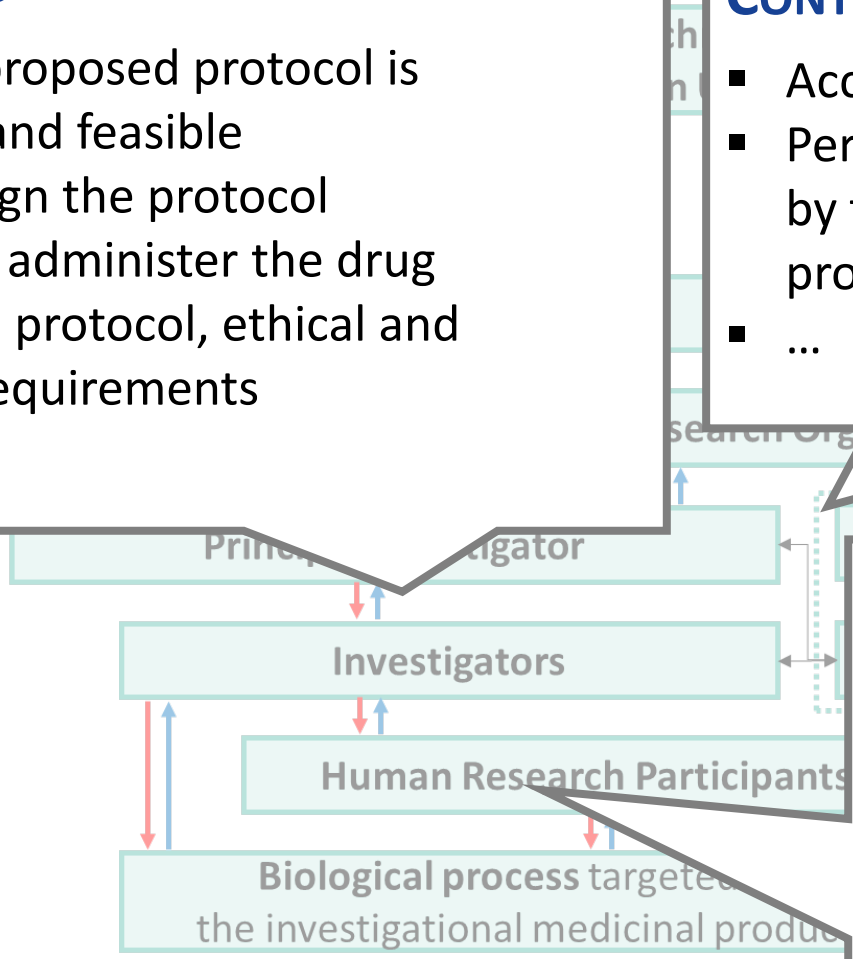
The Safety Control Structure at a high level of abstraction

INVESTIGATORS

- Ensure the proposed protocol is reasonable and feasible
- Agree and sign the protocol
- Prepare and administer the drug
- Comply with protocol, ethical and regulatory requirements
- …

CONTRACT RESEARCH ORGANIZATION

- Accept the proposed protocol
- Perform tasks that have been delegated by the CRO, as specified in the proposed protocol and its related documents
- …



PARTICIPANT

- Make the informed choice to enrolled in the trial
- Follow study requirements
- Inform investigators of any symptoms or adverse events

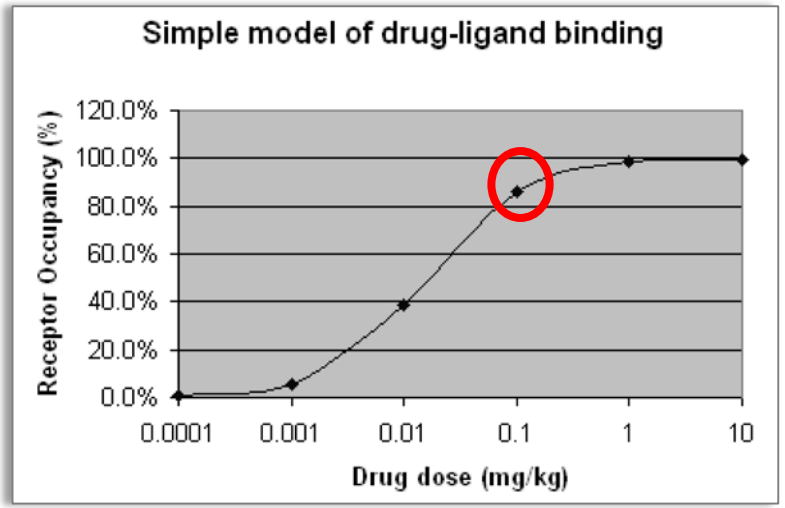
Analysis of the loss at the biological level

What is a cytokine release syndrome?

- An **uncontrolled released of interleukins** that activate others immune system cells and provoke the **destruction of the individual's own cells**
- Triggered by a variety of factors such as infections and certain drugs

Why it happen at the biological level? (with hindsight!)

- **A too high starting dose administered to the volunteers**
- The occupancy of CD28 receptor was 86.2% and induced a large release of pro-inflammatory cytokine in human volunteers ('cytokine storm') ESG, 2006



INVESTIGATORS

Unsafe Control Actions

- Administer a toxic dose of drug to the volunteers
- Administer the drug with a too fast pace of administration

Feedbacks

- Volunteers' symptoms
- Investigators’ brochure and protocol provided by sponsor/CRO

Context

- The administered drug complied with the requirements of the protocol, **including the dose, pace of administration and infusion rate**
- The study protocol was **designed by the sponsor**, validated by **the MHRA and IEC** and accepted by **the CRO**

INVESTIGATORS

MENTAL MODEL?

- Who were the “investigators” described in the report?
- What experience, training and qualifications do they had in clinical research, and about in the specific field of immunology?
- What were their knowledge about the “cytokine release syndrome”?

Sponsor (TeGenero AG)

Unsafe Control Actions

- Determine an unsafe starting dose
- Designed a protocol that did not allow the detection of a serious adverse event to the first volunteer before its administration to the next ones

Feedbacks

- MHRA and IEC approvals
- No feedbacks from CRO and investigators

Context

- The preclinical studies complies with guidelines and were adequate
- Dose calculation method was **in accordance with Good Clinical Practice**

Sponsor (TeGenero AG)

Mental model?

ESG, 2006

How the starting dose was calculated ?

1. **No Observed Adverse Effect Level** in animal models and in vitro studies: **50 mg·kg^{-1}**
2. Application of a **correction factor:** **16 mg·kg^{-1}**
3. Application of a **default safety factor**: **1.6 mg·kg^{-1}**
4. Application of an **additional safety margin** of 10 by the sponsor: **0.1 mg·kg^{-1}**

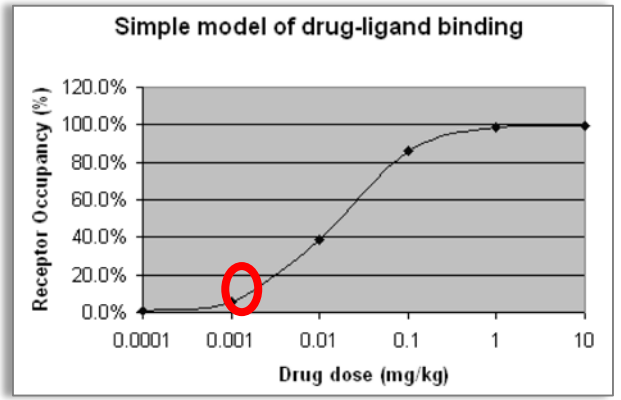
The pitfall

- At any tested dose, the nonhuman primates **did not experience any gross adverse reactions and its lymphocytes did not proliferate when stimulated with TGN1412**
- In *in vitro* studies, TGN1412 did not lead to a such activation of T-cells during

Sponsor (TeGenero AG)

- Dose calculation based on methods developed for "classical" drugs, **not for drugs with "chain reaction effect", such as recombinant antibodies**

"If the Minimal Anticipated Biological Effect Level (MABEL)" was used, "the safe starting dose **would have been** calculated to be **0.005 mg·kg^{-1}** " *ESG report, 2006*



Hindsight bias!

- ✓ MABEL-based approach was first officially introduced in 2007
- ✓ Do not explain why the sponsor's team members have chosen the NOAEL approach…
- ✓ Do not explain why the MHRA and IEC did not advice the sponsor…

An “unpredicted event” or an underestimated likelihood/gravity of such an occurrence?

List of potential adverse events and their treatments

Event	General measures	Specific measures
Anaphylaxis	Airway/circulation support/ vasoconstrictors	Corticosteroids /Beta- agonists / antihistamines
Immunogenicity /Autoimmunity	Avoid further exposure	Steroids/ antihistamines if required.
General cutaneous reactions	Antihistamines, analgesics,	Corticosteroids if necessary
Cytokine release syndrome	General supportive measures	Corticosteroids and other appropriate clinical measures.
serious adverse events	General supportive measures	System specific measures. Stop trial if a number of serious ADRs were reported.
Immunosuppression (massive induction of anti-inflammatory cytokines & / regulatory T cells)	Appropriate counter measures	Antibiotics for infection etc..

Extract of the **study protocol**, from ESG report, 2006, p.32

- The symptoms of CRS are triggered within minutes to hours after infusion Winkler, et al., Blood. 1999
- The dosing pace did not account for the dynamic of CRS…

Initial lessons and perspectives

The current investigation process is certainly open to improvement

- Much missing information
- Focus on “generic” operators and “context-free” decision-making
- Focus on the gap between “work-as done” and “work-as-imagined” but not on why it happen in the particular context of the event

An initiative that foster debates on (actual) safety issues

- How to adapt to change?
- Definition of the Safety Control Structure, as it currently exists
- Communication & Coordination between Controllers
- Better consideration of Human & Organizational factors issues: decision-making, safety culture, trade-off productivity versus safety,…

Disclaimers

The views expressed in this presentation are those of the authors and do not necessarily reflect their respective companies or institutions

Thank you for your attention