A Retrospective of 30+ years in Early Clinical Development

Apologies for errors and omissions!!!

E M Allen and TGK Mant December 2022

Starting out in Early Clinical Development in the 1980-1990s

- **Academic and clinical backgrounds**
  - **Guy's Hospital and Medical School**

  - Colin Dollery, Michael Rawlins,
  - Paul Turner, Jim Ritter
  - Howard Rogers, John Trounce,
  - Roy Spector, Alan Richens,
  - Phil Routledge, Malcolm Lewis,
  - Paul Lietman -Johns Hopkins USA

Early Clinical Development

- Phase 1 healthy volunteer studies were **not regulated** and outside the Medicines Act (1968)
  - › UK favourable environment for US Pharma companies no IND or equivalent required.
  - › ABPI guidance on Phase1 studies 1970, revised in 1977 and in 1988, with the latter update producing two sets of guidelines, one for procedures and one for Phase I facilities.
  - Local ethics approval – expected good practice but **not legally mandated**
  - › Academic departments of clinical pharmacology (e.g., Barts, Cardiff, Dundee, Edinburgh, Bath, Hammersmith, Guys, UCL)
  - › Industry owned units in the UK (ICI, Upjohn, Smith Beecham, Pfizer, Wellcome)
  - › Commercial phase 1 units (e.g., Charterhouse, GDRU, Hazelton, HMR, ICP, Inveresk, Medeval, Simbec)
- ICH E6 Guideline on Good Clinical Practice 1996
  - Guideline only and **not legally mandated**
- Directive 2001/20/EC : Implemented 2004 (GCP and GMP)

Guy's Drug Research Unit 1985 to 2016

Typical Phase I Program

Increasingly, cohorts of the target population are included for proof-of-mechanism/concept/principle

Study type	Dose Levels	Parallel or Crossover
Single ascending dose (SAD)	5–8	Either
Fed: Fasting (if oral)	1	C
Multiple ascending dose (MAD)	3	P
± Drug Interaction	1	C
± Further study to focus on biological effect	1–3	Either
± Bioequivalence of new formulation	1	C

Use of appropriate biomarkers for safety and PD

Occasionally, most of the program can be included in one "umbrella" protocol

Lessons from the past

- **The Death of Niall Rush - An Experiment in James Street, Dublin**
  - 31 August 1984 Derek Dunne (http://politico.ie/archive/death-niall-rush-experiment-james-street)
- **Death of a Medical Student Volunteer in Cardiff (1985)**
  - Aplastic anaemia following participation in a clinical trial investigating the rate of onset of action of different formulations of Midazolam
  - RCP Guidance on studies in non patient volunteers (1986)
  - AICRC (1988)
- **Manchester UK 1990** – Hepatitis B outbreak
- **The Over-Volunteering Protection System (TOPS)** 2002 and adopted by HRA 2013
- **USA 2004 –** Healthy volunteer? Suicide
- **Canada 2005 –** TB outbreak
- **TGN1412 -2006** – Cytokine storm in multiple volunteers
- **BIAL10-2474-2016** – Healthy volunteer death

Paracelsus 1493-1541 - 'All substances are potential poisons. It is the dose which determines whether a substance is a poison or not'

BBC NEWS

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

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Six taken ill after drug trials

The six are being treated at Northwick Park hospital

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 within hours of taking it.

Eight volunteers were involved, but two were given a placebo at the unit which is on Northwick Park Hospital's grounds but is run independently.

"**This is an absolutely exceptional occurrence - I cannot remember anything comparable**"
Richard Ley, Association of the British Pharmaceutical Industry

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

BBC LONDON
Travel, features and more from the BBC website for London

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BIA10-2474 trial – January 2016

BIA10-2474 inhibits a serine protease, fatty acid amide hydrolase (FAAH), distributed widely in brain and other organs

FAAH inhibitors are a known class of potential medicines with analgesic and anti-inflammatory properties in animal models.

BIA 10-2474 started development for neuropathic pain with FIH study at a well-respected and experienced phase 1 CRO in Rennes, France

However, during the FIH study one subject died and five others were hospitalized

BIA 10-2474 caused sudden damage to very specific CNS symmetrical structures, possibly involving micro-hemorrhages and possibly related to cumulative total dose of drug

EMA Committee For Medicinal Products For Human Use (CHMP)

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

- Came into effect 1st September 2007

Message: ***When planning a first-in-human clinical trial, sponsors and investigators should identify the factors of risk and apply risk mitigation strategies accordingly as laid down in this guideline.***

  - › Early access to advice for both regulators and sponsors
  - › Determining and administering the initial doses in man
    - » ***Sentinel groups***
    - » ***Dose stagger***
    - » ***Starting dose estimation***
    - » ***MABEL/PAD vs NOAEL***
  - › The clinical environment for first in man studies
  - › Developing the skills and training to meet future needs

MHRA Phase 1 Voluntary Accreditation Scheme

- Came into operation in 2010
- First-in-human trials should take place
  - In appropriate clinical facilities
  - Emergency and resuscitation facilities
  - Conducted by trained and experienced Investigators

- Principal Investigators for FIH trials
  - Have relevant clinical experience in running Phase I trials,
  - A post-graduate qualification, such as a Diploma in Human Pharmacology, DPM, MSc in Clinical Pharmacology or equivalent.

Revised EMA guidance on early phase studies 2018

- More rigorous preclinical pharmacology evaluation
  - › Mechanism, efficacy, dose response, selectivity(on and off target), species specificity
  - › Identify the degree of uncertainty around a compound and provide risk mitigation strategies
  - › Estimate the therapeutic dose range and do not significantly exceed this
  - › Covers single and multiple dosing
    - » Sentinel dosing strategy in both
  - › **Utilization of emerging PK and PD data to inform dosing strategy**
  - › **Maximum tolerated dose objective no longer acceptable in healthy volunteers**
  - › Timelines
  - › Cost

Safety record of Phase 1

- INCIDENCE of SAE in young = 0.3%,
- 0.02% “worrying”
- Life threatening ?
- Severe ?
- In the literature, only 15 deaths have been published during the last 40 years in Western countries, although probably 100,000 healthy subjects are dosed every year; moreover, only four deaths could not have been avoided if accurate common rules had been strictly adhered to.

INCIDENCE of DEATH = 1:1,000,000?

Adapted from Sibille et al, Br J Clin Pharmacol. 2006 October; 62(4): 502–503, (updated with death reported in 2016)

New Legislation as a result of BREXIT

- **The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019**
- **Medicines and Medical Devices Act (2021) – received Royal Assent Feb 11 2021**
- **UK will continue to be a major player in the conduct of Phase1 studies**
  - Reputation for scientific innovation and development
  - Global recognition of MHRA expertise and rigour
  - Similar regulatory requirements to EMA CTR
  - New regulatory process up and running and seen as less complex

    and burdensome
  - Favourable timelines

Going forward - Change is inevitable

There is nothing permanent except change – Heraclitus

- **Better understanding of the pathological basis of disease**
  - Immunopharmacology, genetics and epigenetics
    - › Understanding signalling and cascade pathways
    - › New drug targets
- **Study designs**
  - Complicated adaptive flexible hybrid designs
    - › e.g. Phase1 and 2a combined
  - Use of onsite and remote technologies
- **Risk/Benefit**
  - Transparency and honesty
  - More collaboration academia /NHS/ Pharma

- **The development of new and better medicines is vital for the public health**
- **The ‘first in human trial’ is the gateway between biological research and clinical medicine**

- ***Professor Sir Gordon Duff - Presentation May 2008***

- ***Thank you for listening***

- ***Questions ?***