

Impact of the EU Directive in the UK

Steve Warrington

Medical Director

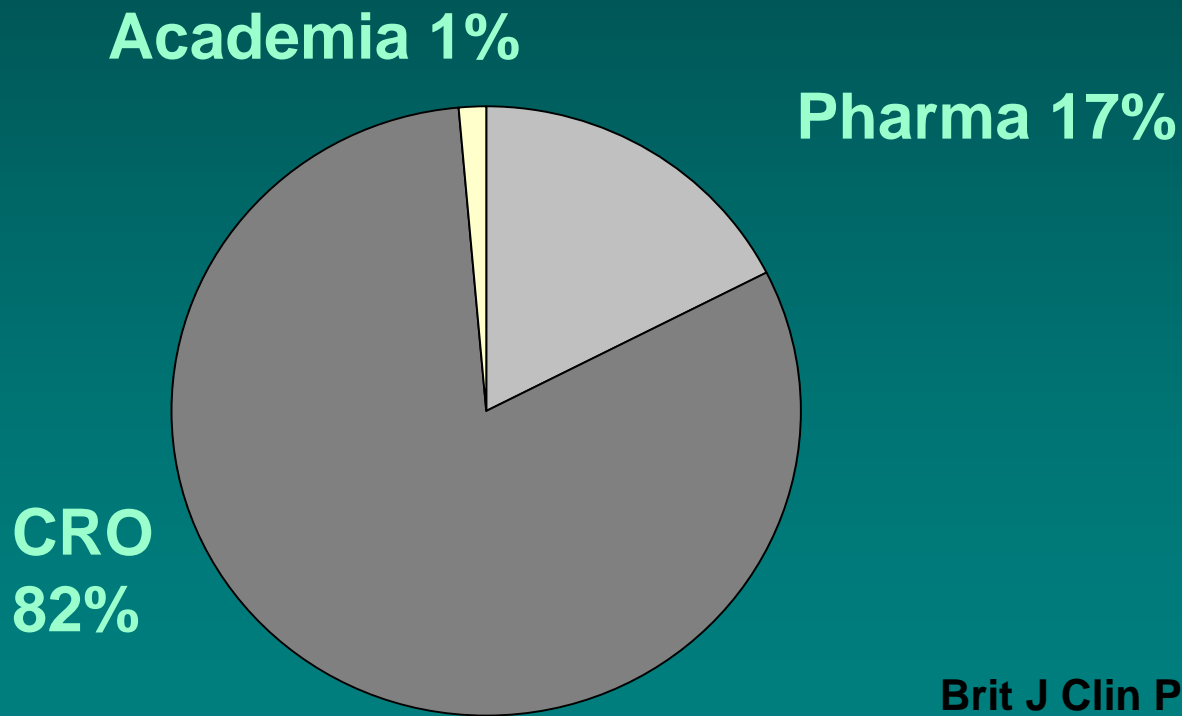
HMR



Who does UK phase 1 trials?

AHPPI survey of 29 commercial UK phase 1 units, 1999–2000

1235 trials



Brit J Clin Pharm 2003

Regulation of phase 1 trials: before 1 May 2004

- no MHRA review — *no therapeutic benefit to subject*
- trials controlled by sponsor and investigators
- ethics committees
- guidelines – GCP, ABPI,
Royal College of Physicians

...after 1 May 2004

- need approval by MHRA (CTA) & 'phase 1 REC'
- MHRA and REC response:
 - applications in 60 days
 - substantial amendments in 35 days
- MHRA enforces GCP and GMP by inspection

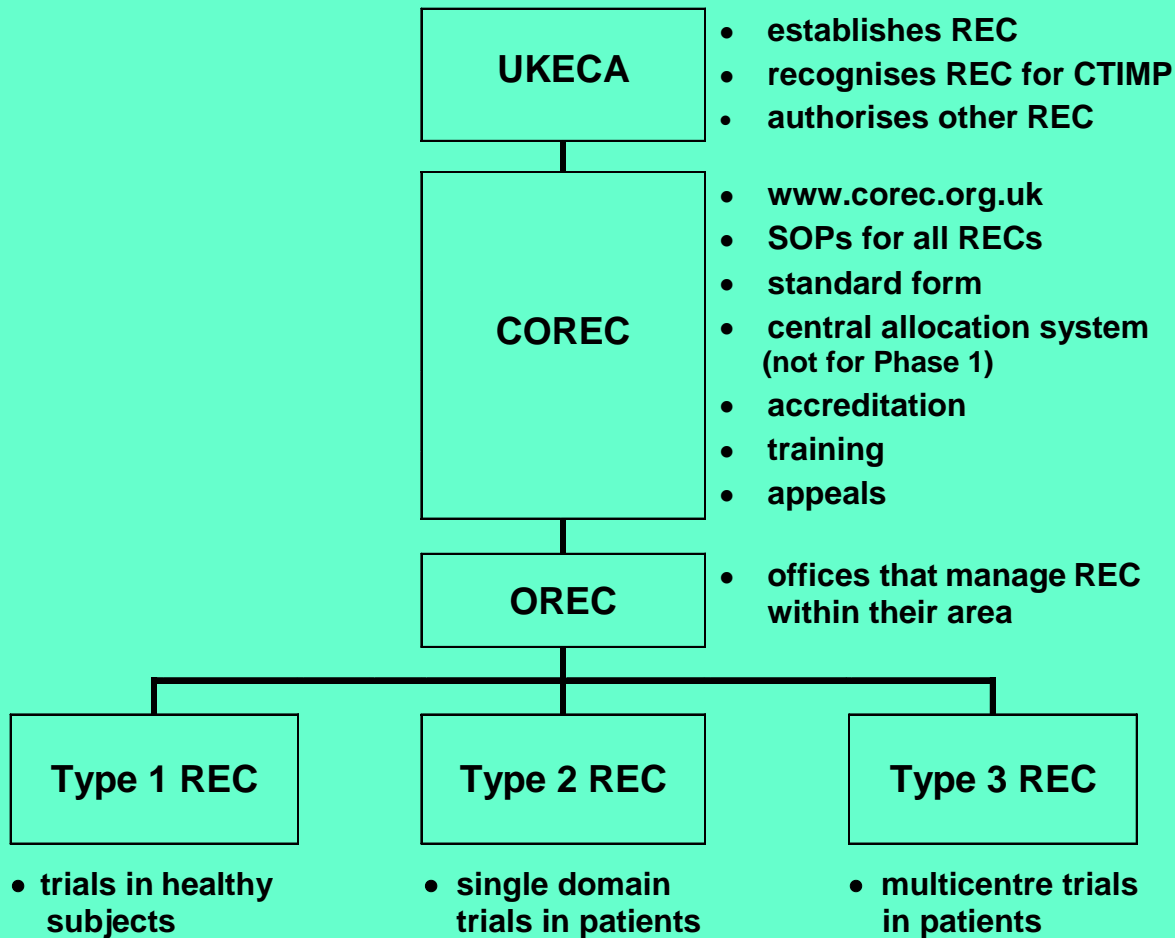
...after 1 May 2004

- manufacturing, assembling or importing IMP needs a Manufacturer's Authorisation
- MA(IMP) holder:
 - follows GMP
 - uses Qualified Person (QP) to certify each IMP batch
- Sponsor needs EudraCT no & gives safety data to MHRA and REC

CTA – the MHRA's record

- MHRA target: respond within:
 - mean 14 days
 - maximum 21 days(matches AHPPI survey of REC response time)
- so far, MHRA is meeting those targets

REC system in the UK



Substantial amendments are likely to have a significant impact on:

- safety, or physical or mental integrity, of trial subjects
- scientific value of the trial
- conduct or management of the trial
- or
- quality or safety of any trial IMP

Substantial amendments

- MHRA response time – up to 35 days
- REC – varies among REC, but most faster than MHRA

Substantial amendments: the sponsors' response

- Flexible protocols
- Sponsor decides what is a substantial amendment

Result:

- few substantial amendments

Phase 1 pharmacy work: before 1 May 2004

- batches prepared on site, often just before administration
- pharmacist not always involved – doctor or nurse do preparation
- often no PSF – certificate of analysis sufficient

Phase 1 pharmacy work: before 1 May 2004

- no QP
- no MA(IMP)
- auditing to GCP, not GMP

Pharmacy after 1 May 2004

SI 1031: Part 6

Manufacture and importation of IMPs

- Regulation 36(1)
-no person shall manufacture, assemble or import any IMP except in accordance with an authorisation granted by the licensing authority..... (“a manufacturing authorisation”)

SI 1031: definition of manufacture

- “manufacture” of an IMP:

any process in making the product

but not

dissolving, dispersing, diluting or mixing
with vehicle

SI 1031: definition of assemble

“assemble” an IMP:

- enclose IMP in a container which is labelled before the product is used in a clinical trial

or

SI 1031: definition of assemble

- if IMP is already in the container in which it is to be supplied for a trial, labelling the container before the product is used in the trial

Phase 1 pharmacy accepting responsibility for IMP needs:

- quality system based on GMP and GCP
- qualified and experienced staff
- inspection by MHRA for **MA** to manufacture, assemble or import IMP
- the right environment – temperature, air flow control & filtering
- isolators
- purpose-built pharmacy



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Summary of main changes to phase 1 trials

- CTA
- MHRA inspections
- more emphasis on GMP
- MA(IMP) & QPs to assemble IMP
- REC recognised for phase 1 trials in healthy subjects
- substantial amendments go to REC & MHRA



Researchers drowning in bureaucracy

Ethics committees are out of control and discouraging research p241, p277, p280, p282, p286, p288

Reducing complications after cardiac surgery p258

Pluses and minuses of fine needle aspiration p244, p290

Cannabinoids in multiple sclerosis p253

Treating the HELLP syndrome p270

Is it mad to screen every American for mental illness? p292