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Trials of complex interventions in a complex environment

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Emergency medicine



Trials in emergency medicine

- Theory: what defines emergency medicine?
- Practical experience of undertaking trials
- Ethical issues



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What is emergency medicine?



Time is the defining feature of emergency medicine

- Time determines effectiveness
- Treatment benefit is typically time dependent
- Treatment harm is typically independent of time
- Effectiveness typically decreases with increasing time delay

Clinical Trials in EM

- Aim to estimate effectiveness of emergency interventions
- Time delay is an important factor in estimating effectiveness
- Should we seek to control (minimise or optimise) time delay?

What is the aim of the trial?

- Efficacy: To determine whether the intervention can work in optimal conditions
- Effectiveness: To determine whether the intervention does work in routine conditions



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Emergency Medicine Trials

- Efficacy: Minimise all time delays
- Effectiveness: Incur typical time delays of routine practice

Time Delays in EM Research

- Research delays: e.g. applying selection criteria, baseline assessment, informing patient, gaining consent
 - always need to be minimised
- Practice delays: e.g. triage, waits for nursing and medical assessment, administration of treatment
 - minimise in efficacy trials

Research-related time delays

- Need to be avoided in efficacy and effectiveness trials
- BUT, time is needed for participants to make a fully informed decision and give consent



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Patient autonomy

v

Optimal trial design

Patient autonomy

- Does a patient have capacity to make an autonomous decision in an emergency?
- If they have capacity, what is the “right” amount of information to give?
- Can incapacitated patients be recruited to a trial in an emergency without prior consent?

Mental Capacity

The ability to:

- understand the information relevant to the decision
- retain that information
- use or weigh that information as part of the process of making the decision
- communicate the decision

The Legal Framework

- Declaration of Helsinki
- EU Clinical Trials Directive, Medicines for Human Use (Clinical Trials) Regulations, Good Clinical Practice
- Mental Capacity Act

MHRA Inspection Report

Major finding: Obtaining written informed consent. Declaration of Helsinki – “The physicians should then obtain the subject’s freely-given informed consent, preferably in writing.”

Declaration of Helsinki

“Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population.”

Declaration of Helsinki

“In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee.”

Declaration of Helsinki

“Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.”

Good Clinical Practice

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

Mental Capacity Act

Research on a person who lacks capacity to consent is unlawful unless it is:

- Approved by an appropriate body
- Undertaken in accordance with sections 31, 32 and 33 of the Act



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Mental Capacity Act

- Section 31: Requirements for approval
- Section 32: Consulting carers
- Section 33: Additional safeguards



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Consent in Practice

- Written informed consent
- Verbal consent
- Personal legal representation
- Professional legal representation
- Recruitment before consent



Providing information

- Give participants as much information as they can accurately retain
- Individualise provision of information
- Information that is given but not recalled, or given but inaccurately recalled, may be harmful
- Involve patients in decision-making as much as they are willing and able to participate

Initial brief / delayed full

Initial brief information:

- Randomised, control, placebo
- What intervention involves
- Risks and side effects

Delayed full information:

- Data protection and confidentiality
- Rights and complaints procedures
- Follow-up



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Examples

- The RATPAC Trial
- The 3Mg Trial
- The CRASH2 Trial



The RATPAC Trial

- RCT of point of care cardiac markers for low risk acute chest pain
- Participants are well and have full capacity
- All are given the full information sheet
- All must give written informed consent

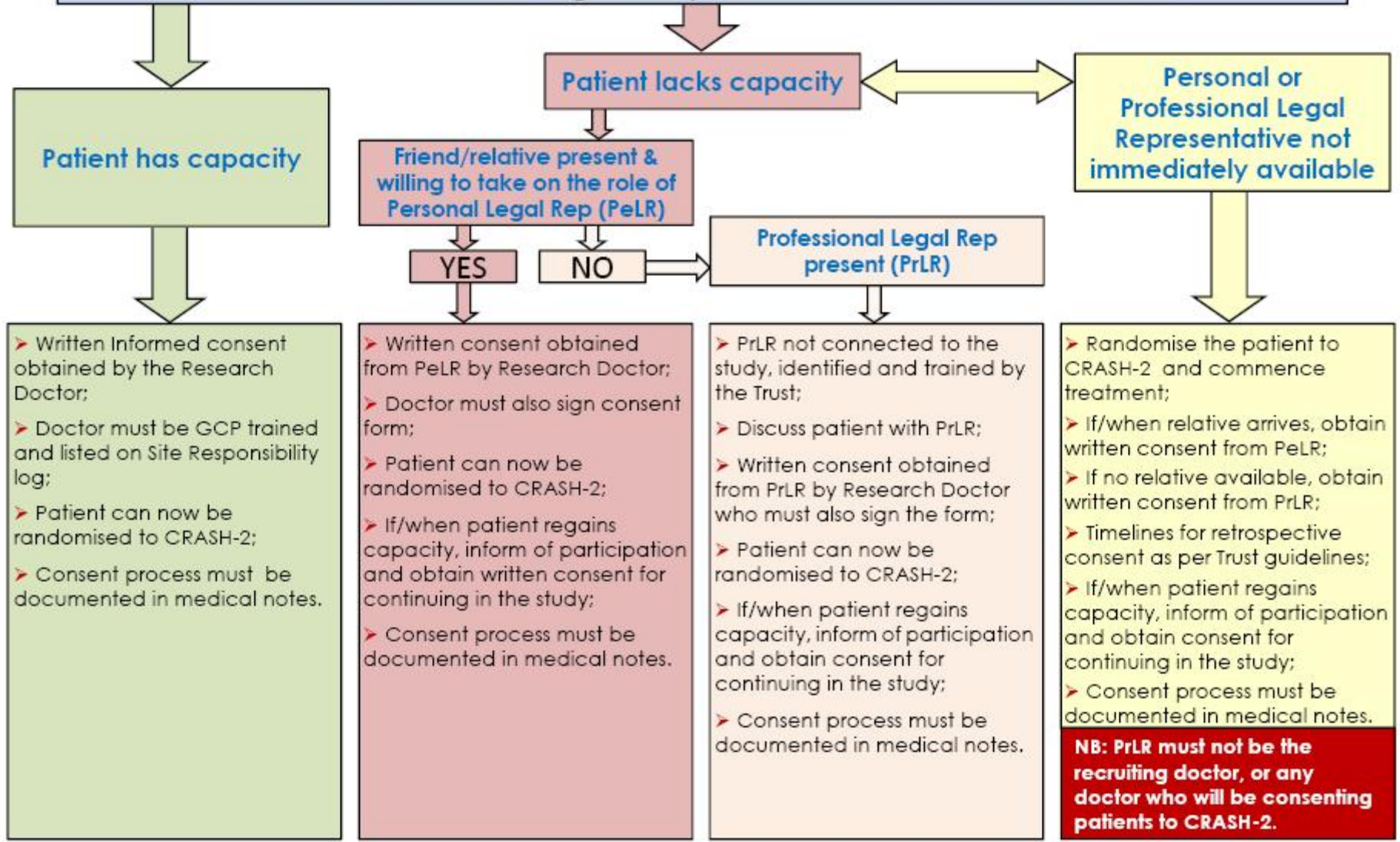
The 3Mg Trial

- RCT of IV or nebulised magnesium sulphate in acute severe asthma
- Participants are acutely unwell but have capacity
- Initial one-side information sheet
- Must give consent but initially may be verbal

The CRASH2 Trial

- RCT of tranexamic acid for life threatening traumatic haemorrhage
- Variable clinical state: range from unwell but with capacity to unconscious
- Exclusion of sickest would exclude those most likely to benefit

Patient fulfils Eligibility Criteria for CRASH-2



➤ Written Informed consent obtained by the Research Doctor;

➤ Doctor must be GCP trained and listed on Site Responsibility log;

➤ Patient can now be randomised to CRASH-2;

➤ Consent process must be documented in medical notes.

➤ Written consent obtained from PeLR by Research Doctor;

➤ Doctor must also sign consent form;

➤ Patient can now be randomised to CRASH-2;

➤ If/when patient regains capacity, inform of participation and obtain written consent for continuing in the study;

➤ Consent process must be documented in medical notes.

➤ PrLR not connected to the study, identified and trained by the Trust;

➤ Discuss patient with PrLR;

➤ Written consent obtained from PrLR by Research Doctor who must also sign the form;

➤ Patient can now be randomised to CRASH-2;

➤ If/when patient regains capacity, inform of participation and obtain consent for continuing in the study;

➤ Consent process must be documented in medical notes.

➤ Randomise the patient to CRASH-2 and commence treatment;

➤ If/when relative arrives, obtain written consent from PeLR;

➤ If no relative available, obtain written consent from PrLR;

➤ Timelines for retrospective consent as per Trust guidelines;

➤ If/when patient regains capacity, inform of participation and obtain consent for continuing in the study;

➤ Consent process must be documented in medical notes.

NB: PrLR must not be the recruiting doctor, or any doctor who will be consenting patients to CRASH-2.

EM: Individuals or Groups?

- Clinical trials guide treatment of individual patients in an emergency
- Trials may also be used to address questions of service organisation and delivery
- This involves evaluating management of groups of patients

What is an emergency?

- Effectiveness of treatment is time critical
- Outcomes of emergencies are often subjective: pain, discomfort, disability, anxiety
- Measurement of effectiveness is often subjective
- Definition of an emergency is subjective

What is an emergency?

- Potentially almost anything!
- Need prioritisation to determine what is the most urgent emergency
- Prioritisation is the other defining feature of emergency medicine

Implications

- Need to evaluate the effect of intervention upon the whole population, not just the target group
- Any emergency intervention can have knock-on effects for other emergencies
- Particularly if intervention involves service reorganisation



Cluster Trials

- Important role in EM research
- Evaluate interventions at group level
- Measure overall effect (not just selected cases)

Unit of Randomisation: Time

- Hours, days, weeks or months can be randomised
- Examples:
 - Trial of the Sheffield Chest Pain Unit
 - Paramedic practitioners
 - Trial of the “A&E physician”

Loss of allocation concealment

- Patients don't usually choose to have an emergency at a particular time
- Staff may select patients into a trial depending upon allocation
- Solution: base selection process on independent assessment, e.g. reception
- And/or make selection process very explicit

Table 1 Application of each exclusion criterion by group. Values are numbers (percentages) unless otherwise indicated

	All patients (n=6957)	Patients attending		Odds ratio
		Chest pain observation unit days (n=3451)	Routine care days (n=3506)	
Changes to the electrocardiogram that are diagnostic for acute coronary syndrome	764 (11.0)	361 (10.5)	403 (11.5)	0.90
Clinically diagnosed unstable angina	2402 (34.5)	1203 (34.9)	1199 (34.2)	1.03
Comorbidity or serious alternative cause	869 (12.5)	424 (12.3)	445 (12.7)	0.96
Age <25 years	444 (6.4)	238 (6.9)	206 (5.9)	1.19
Negligible risk of acute coronary syndrome	847 (12.2)	427 (12.4)	420 (12.0)	1.04
Trial specific exclusion criteria	513 (7.4)	243 (7.0)	270 (7.7)	0.91
Eligible to consent	1118 (16.1)	555 (16.1)	563 (16.1)	1.00

Summary points

EM involves time critical interventions

- Management of time delay depends on the research question
- Conflict between respect for patient autonomy and optimal trial design
- The legal framework does not prevent recruitment of incapacitated patients in an emergency

EM involves prioritisation of patients with conflicting needs

- Measure effect of intervention upon all patients