Clinical Trials in Emergencies:

When consent might kill you

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EFGCP Regional Conference on Hot Topics in Clinical Research
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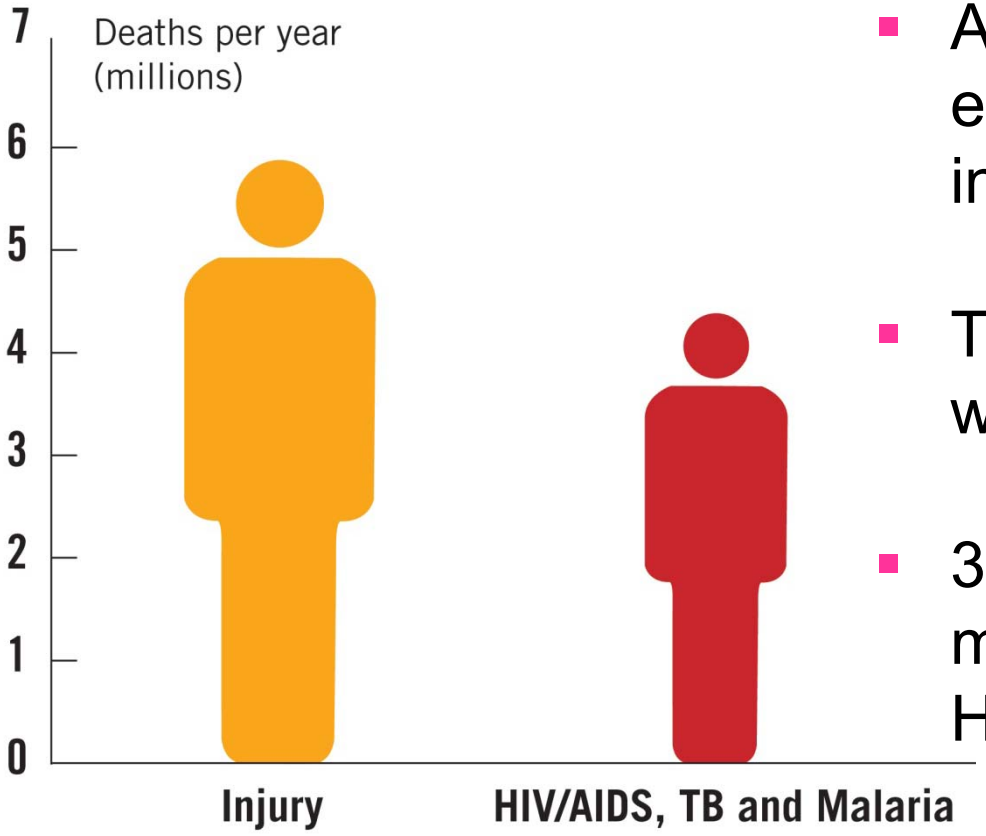
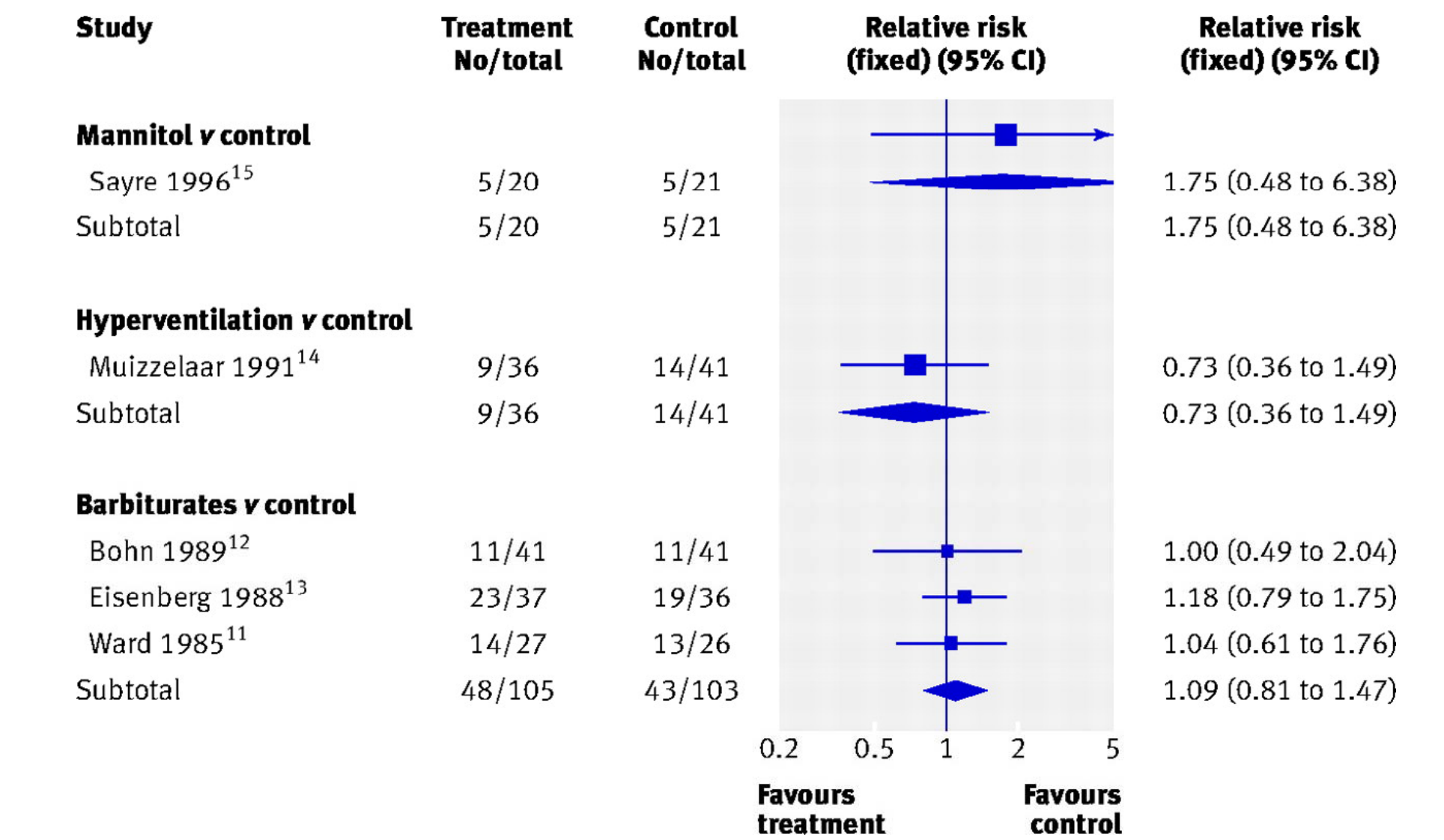
Burden of Injuries



- About 5.8 million people die each year as a result of injuries.
- This accounts for 10% of the world's deaths
- 32% more than deaths from malaria, tuberculosis and HIV/AIDS combined.

Commonly used treatments for TBI



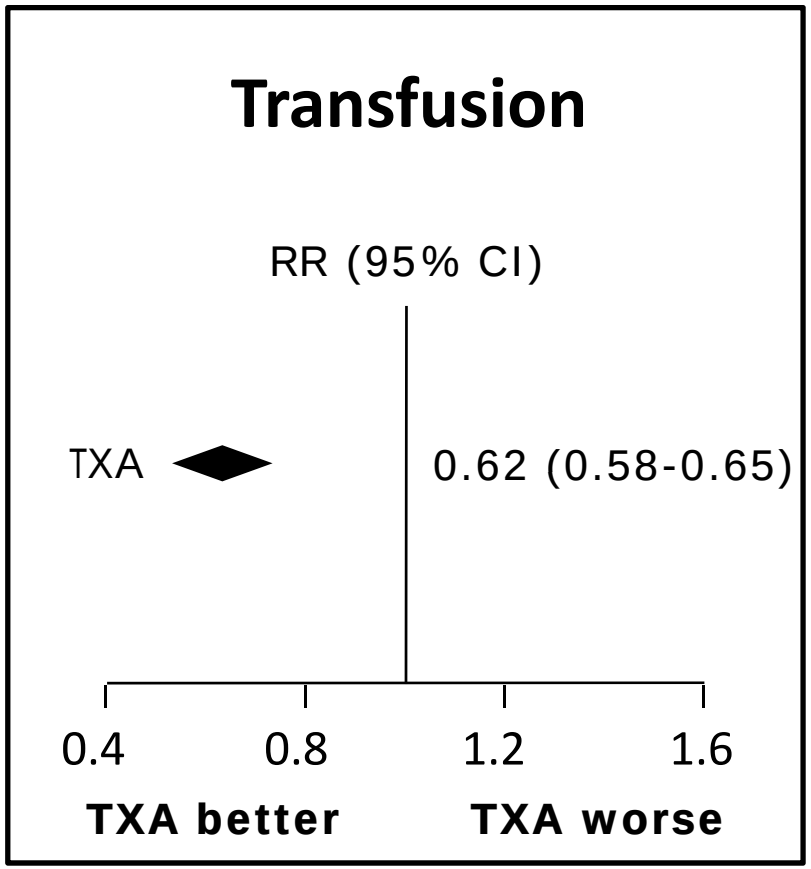
Study	Treatment No/total	Control No/total	Relative risk (fixed) (95% CI)	Relative risk (fixed) (95% CI)
Mannitol *v* control				
Sayre 1996[15]	5/20	5/21		1.75 (0.48 to 6.38)
Subtotal	5/20	5/21		1.75 (0.48 to 6.38)
Hyperventilation *v* control				
Muizzelaar 1991[14]	9/36	14/41		0.73 (0.36 to 1.49)
Subtotal	9/36	14/41		0.73 (0.36 to 1.49)
Barbiturates *v* control				
Bohn 1989[12]	11/41	11/41		1.00 (0.49 to 2.04)
Eisenberg 1988[13]	23/37	19/36		1.18 (0.79 to 1.75)
Ward 1985[11]	14/27	13/26		1.04 (0.61 to 1.76)
Subtotal	48/105	43/103		1.09 (0.81 to 1.47)

The effect of corticosteroids was a highly significant relative increase of 18% in all cause mortality


CRASH 2
Clinical Randomisation of an Antifibrinolytic
in Significant Haemorrhage

TXA use in surgery

TXA reduces bleeding in surgery

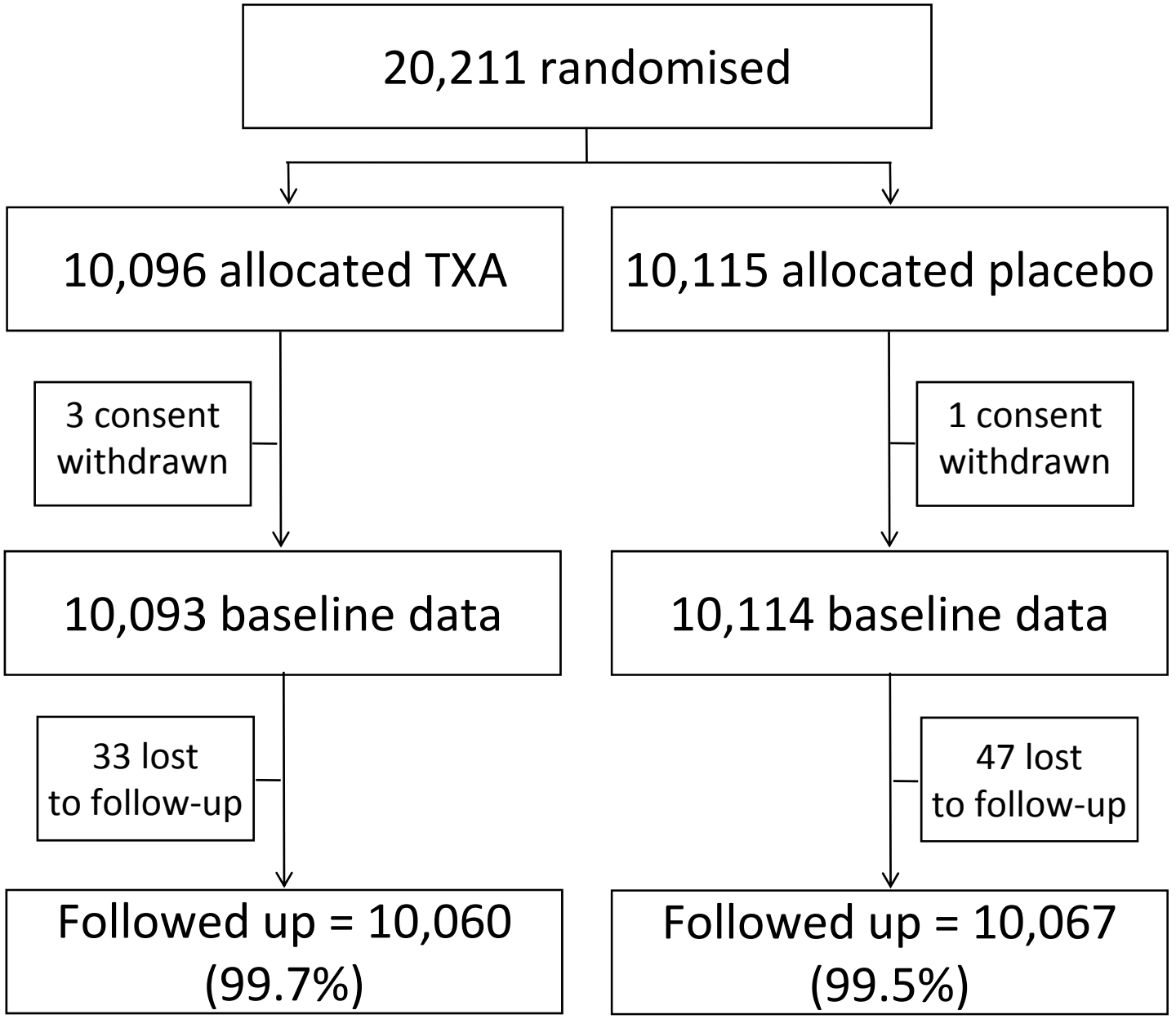


95 trials

72 trials

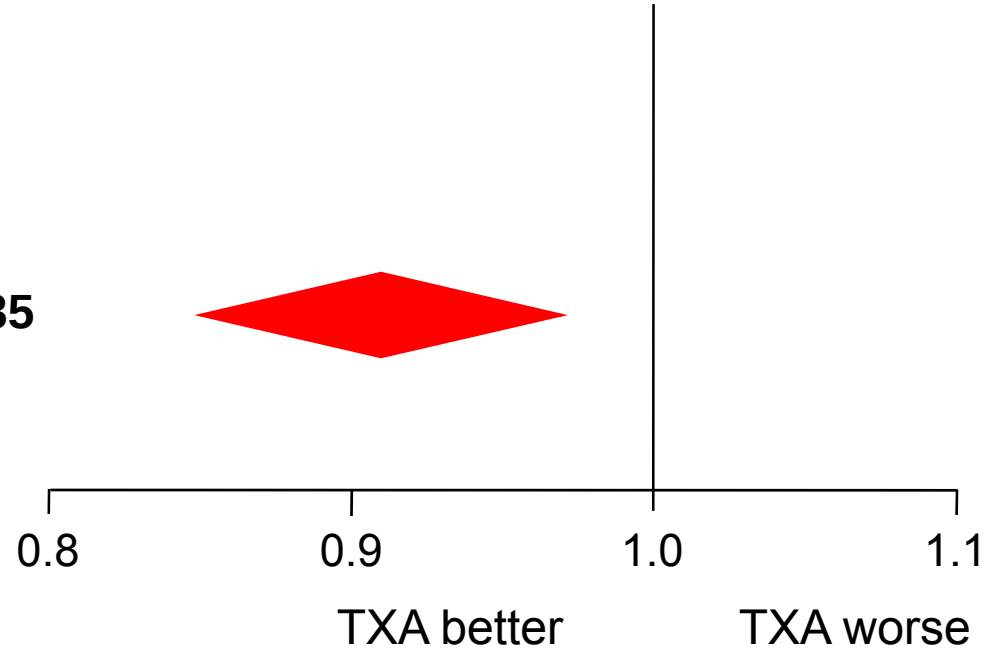
Ker et al. BMC Emergency Medicine 2012, 12:3

CRASH-2 trial profile



Any cause of death

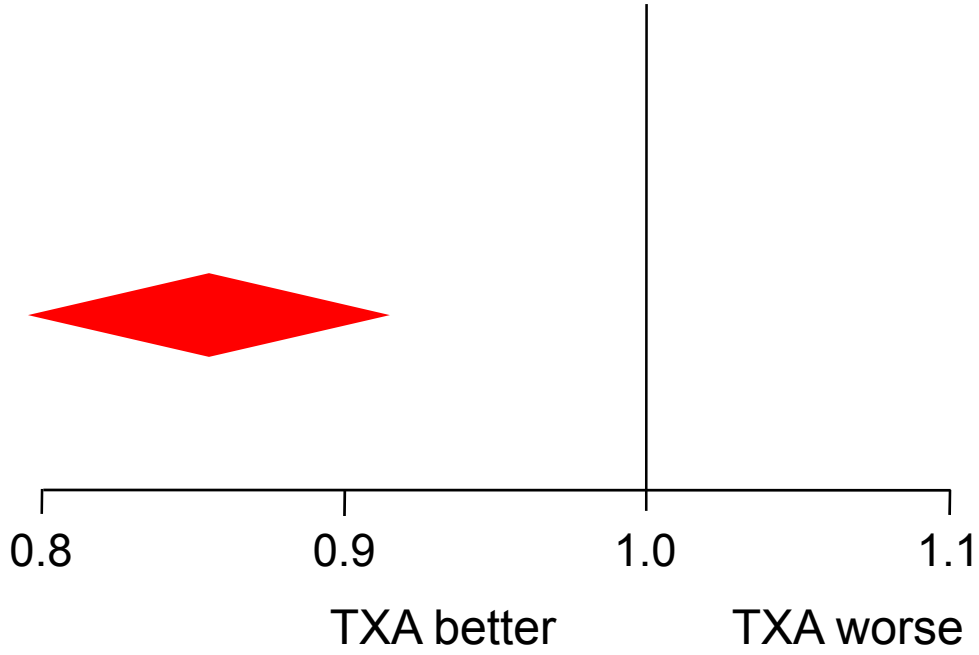
TXA (n=	**Placebo (n=**	RR (95% CI)
1,463 (14.5%)	1,613 (16.0%)	
0.91 (0.85–0.97) 2P=0.0035		



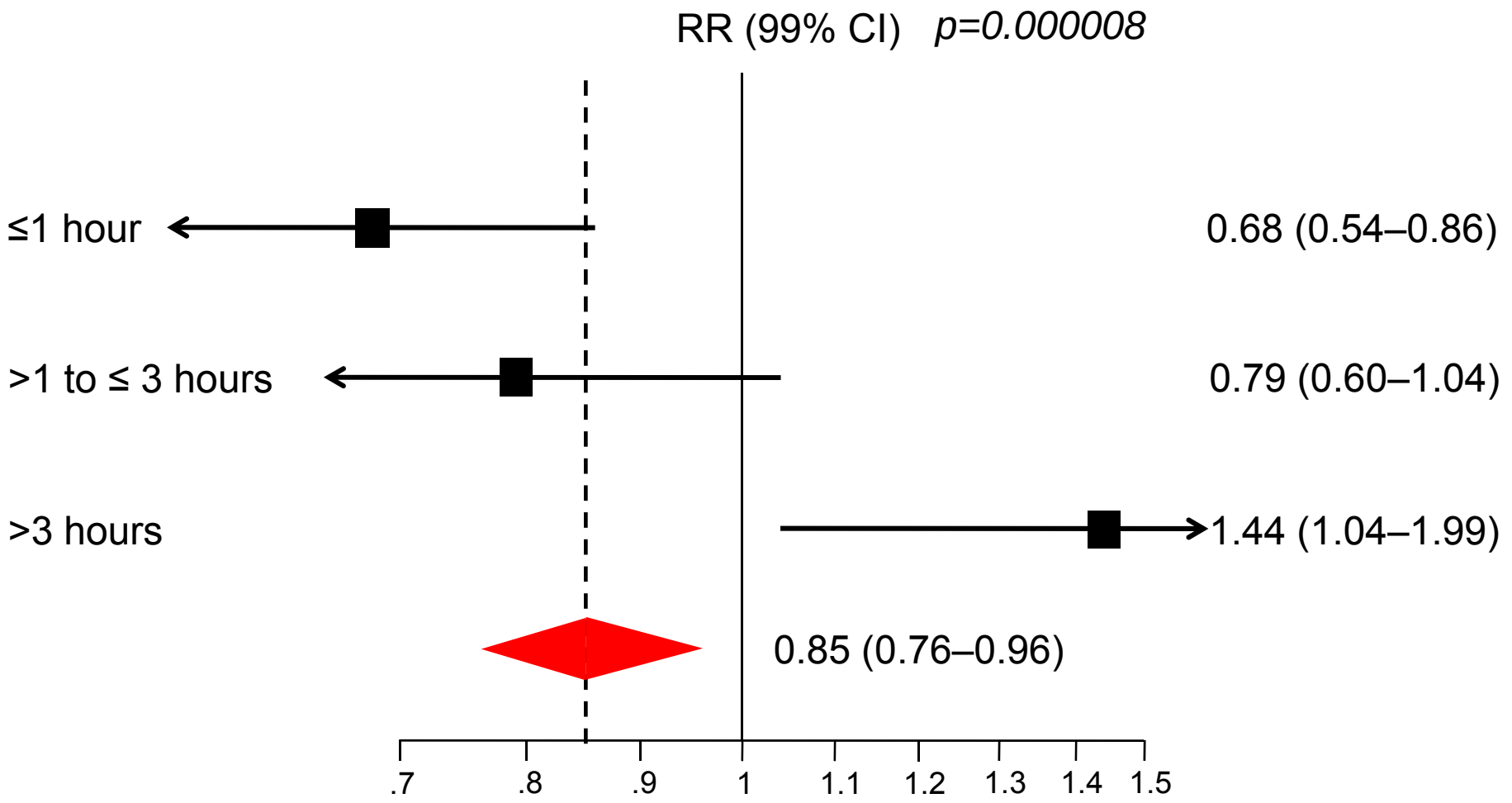
Death due to bleeding

TXA	**Placebo**	RR (95% CI)
(n= 10,060)	**(n= 10,067)**	
489 (4.9%)	574 (5.7%)	

0.85 (0.76–0.96) 2P=0.0077



Bleeding death: early treatment is better



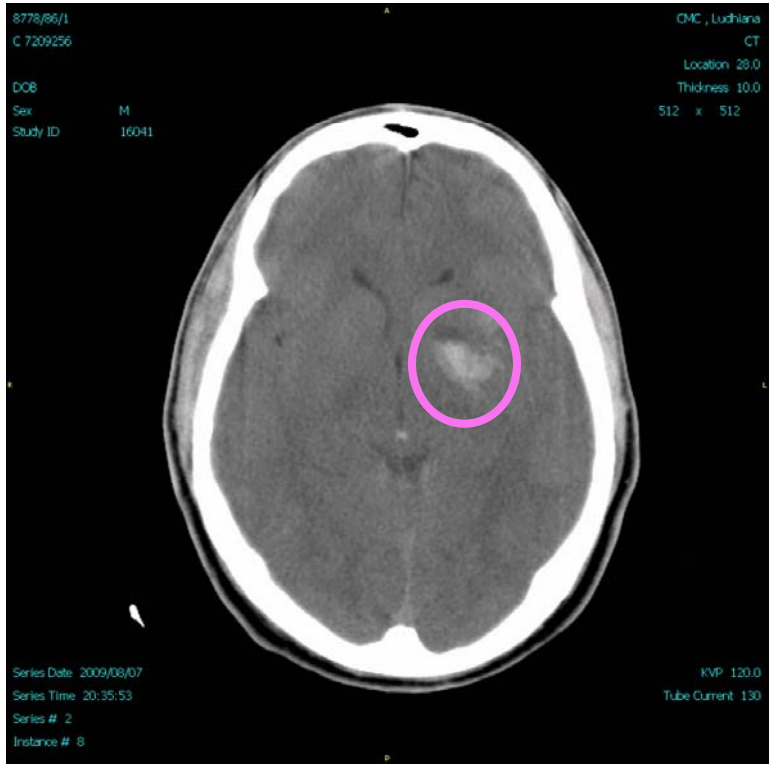
WAIVER OF CONSENT VS REQUIREMENT FOR REPRESENTATIVE CONSENT

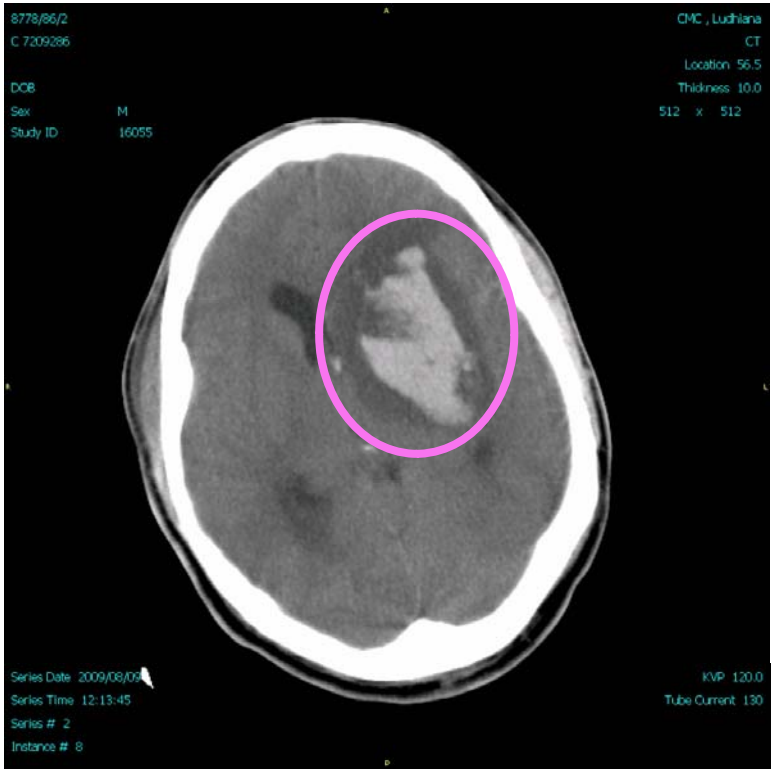
- 116 hospitals – 40 countries
- 4000 patients randomised
- 78 hospitals REC approved Waiver of Consent
- 38 hospitals REC approved Requirement for Representative Consent

	Waiver of Consent	Required Consent from a representative	Difference
Time to randomisation (hours)	3.2 (SE 0.16)	4.4 (SE 0.21)	1.2 hours (p,0.0001)
Average recruitment rate per month	2.0 (SE 0.29)	1.5 (SE 0.24)	0.51

Research in emergency situations: with or without relatives consent. The CRASH Trial Management Group: ***Emerg Med J*** 2004; 21:703.

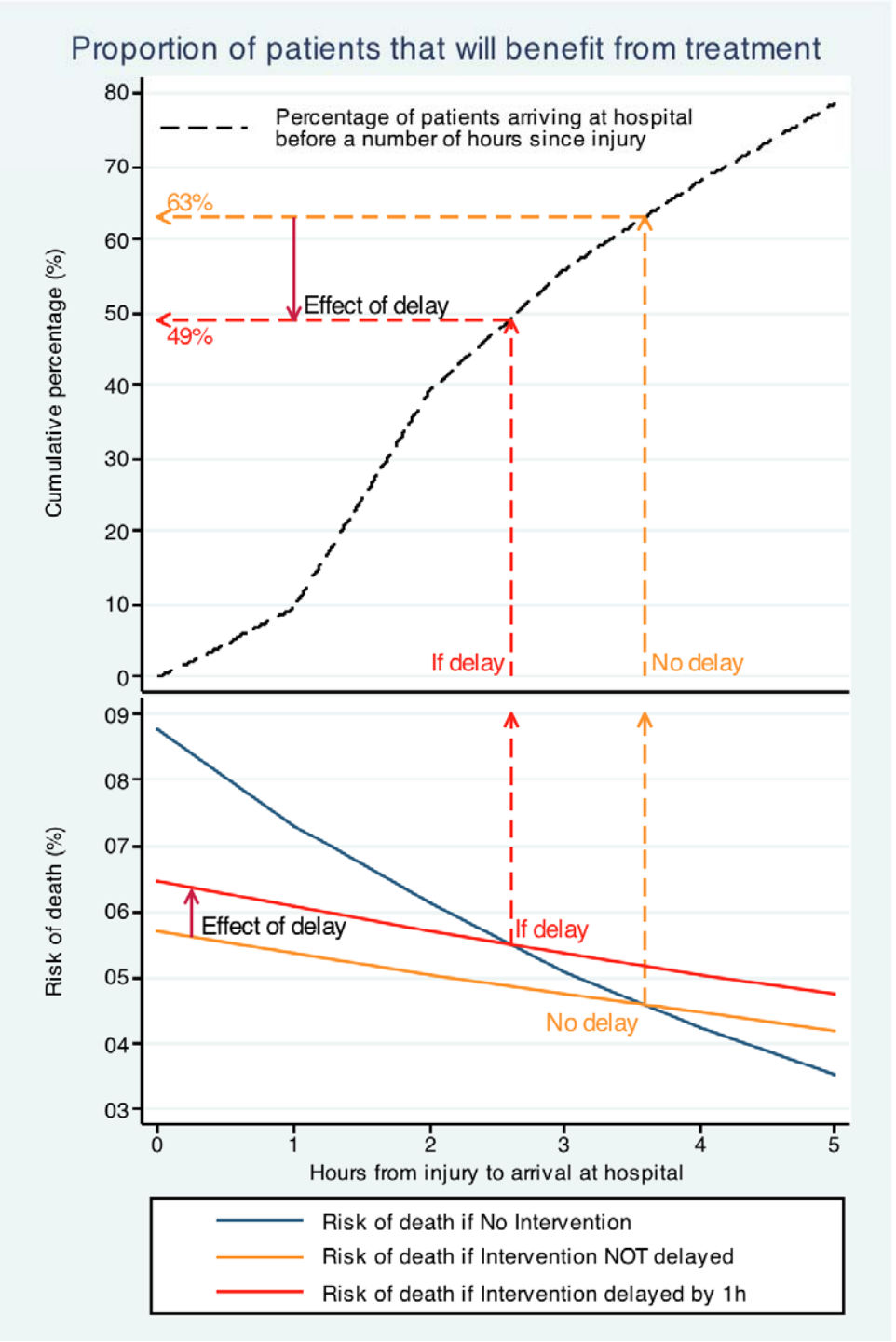
What is happening while we wait?





Effect of consent rituals on mortality in emergency care research. Lancet March 24, 2011

"we estimate that a 1 hour treatment delay reduced the proportion of patients who benefit from the trial treatment from 63% to 49%."



Medicines for Human Use Clinical Trials Regulations

Amendment (No. 2) 2006

If treatment is being, or is about to be, provided for a subject who is an incapacitated adult as a matter of urgency and, having regard to the nature of the clinical trial and of the particular circumstances of the case …..

Recovery of competence

If and when a participant on whose behalf either a personal or professional legal representative has given consent to participate in a research project recovers competence:

She must be informed of her participation.

Consent must be obtained to the use of biological materials or data in the research.

We have carefully considered the issues of the 34 patients discussed in your letter, in conjunction with my vice-Chair. It appears that in all cases a genuine attempt was made, both to initially obtain proxy consent from a Personal or Professional Legal Representative, and subsequently (where the patient survived and regained competence) from the patient. Our opinion is that it would not be appropriate to exclude the data of these patients from analysis, given the risk of bias in the data this would introduce. The trial was ethically conducted in the context of genuine clinical equipoise, in a clinical setting in which true informed consent from the participant prior to recruitment is usually impossible.

Can relatives give fully informed consent in an emergency?

Ker et al. BMC Emergency Medicine 2012, 12:3
http://www.biomedcentral.com/1471-227X/12/3

BMC
Emergency Medicine

RESEARCH ARTICLE Open Access

Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial

Katharine Ker*, Junko Kiriya, Pablo Perel, Phil Edwards, Haleema Shakur and Ian Roberts

Lives saved with TXA (every year)

TXA < 1 hour = 128,000 lives

TXA < 3hours =112,000 lives