# Cytokine Storm in a first-in-man Phase 1 trial: An on-site, pharmaceutical, major incident

BBC NEWS

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

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## Six taken ill after drug trials

**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.


The six are t
Northwick Pa

Relatives are with the patients, who suffer
failure. Two men are said to be critically ill



Imperial College London

The North West London Hospitals NHS Trust


- March 13th 2006 clinical trial

  - Phase 1 study of a novel moAB
  - first-into-man
  - healthy male volunteers

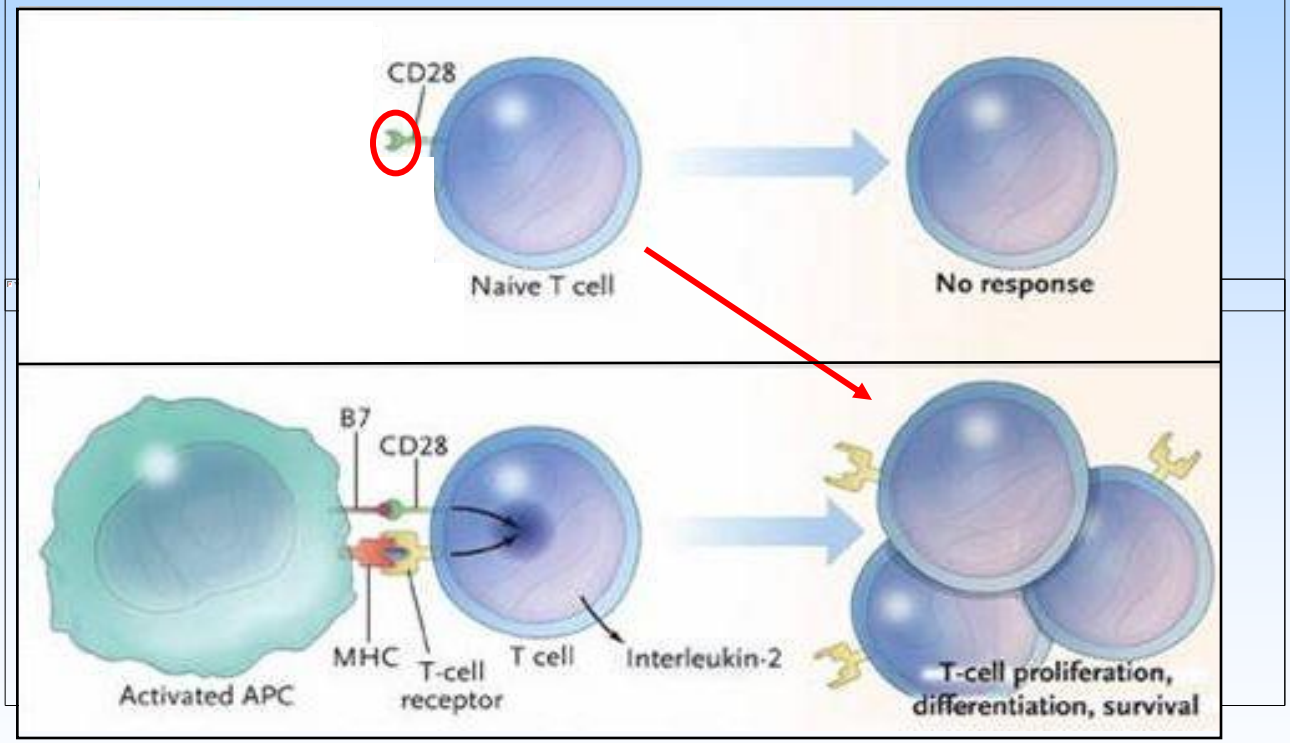
  - randomised
  - placebo-controlled
  - double-blinded

# TGN1412

- Recombinant, humanized, anti-CD28 superagonist monoclonal antibody
- Intended to stimulate $T_{reg}$ cells, modulate inflammatory response

# TGN 1412

- Humanized superagonist anti-CD28 monoclonal antibody (TeGenero AG)




Sharpe AK *et al.* N Engl J Med 2006;355:973-975

TGN1412 infusion

somatic symptoms

T + 50 mins
(30 – 60 min)


systemic inflammatory response

T + 60 mins
(50 - 90 min)

fever, ↓BP

type 1 resp failure, pt 1

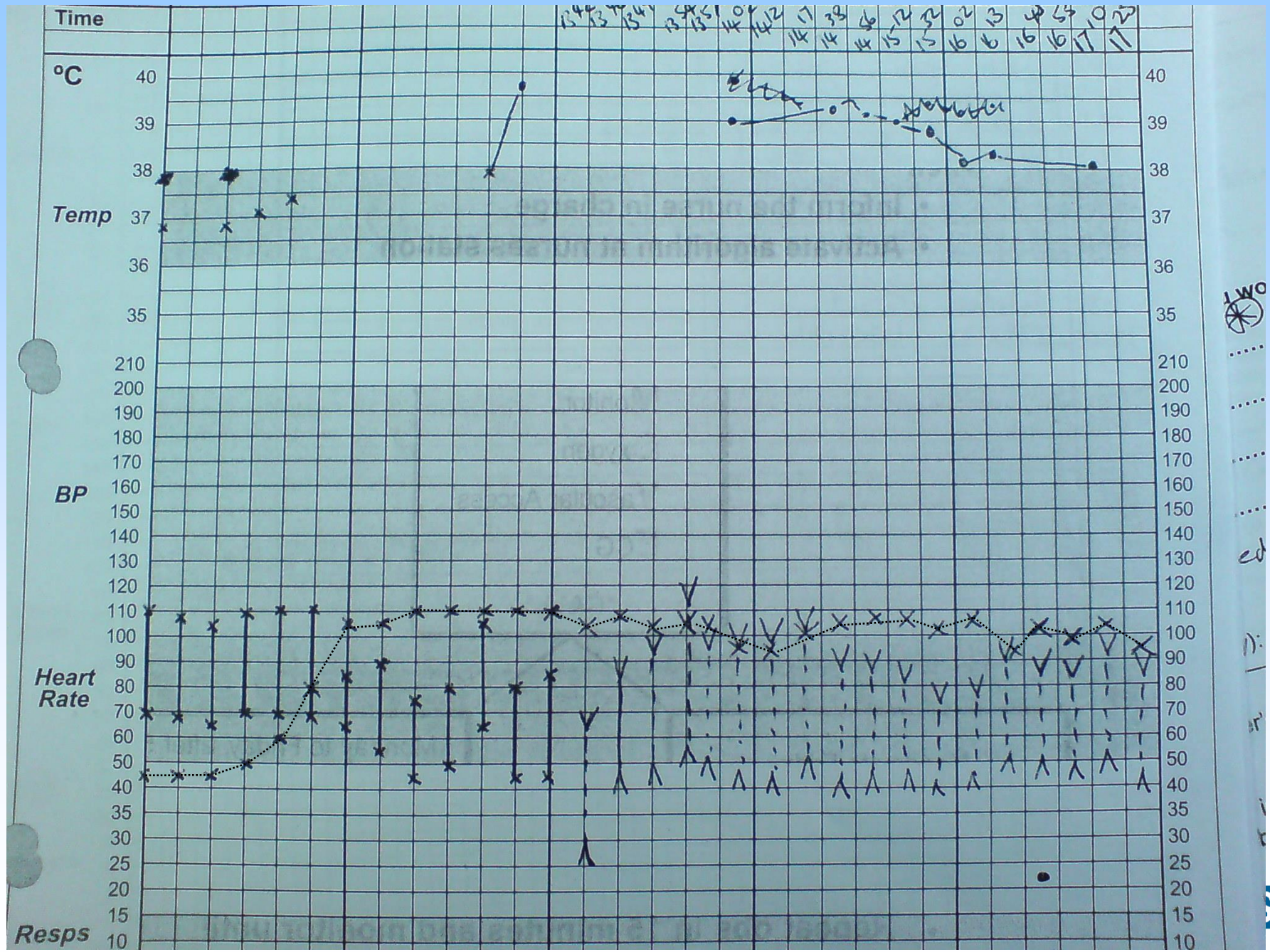
T + 4-5 hours

transient improvement

T + 6-8 hours

Initial Rx

time


Time
°C
Temp
BP
Heart Rate
Resps
40
39
38
37
36
35
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
35
30
25
20
15
10

lab results

T + 8 hours

patient 6
MSOF

T + 10-12 hrs


ICU transfer,
organ support

Rx immune
modulation

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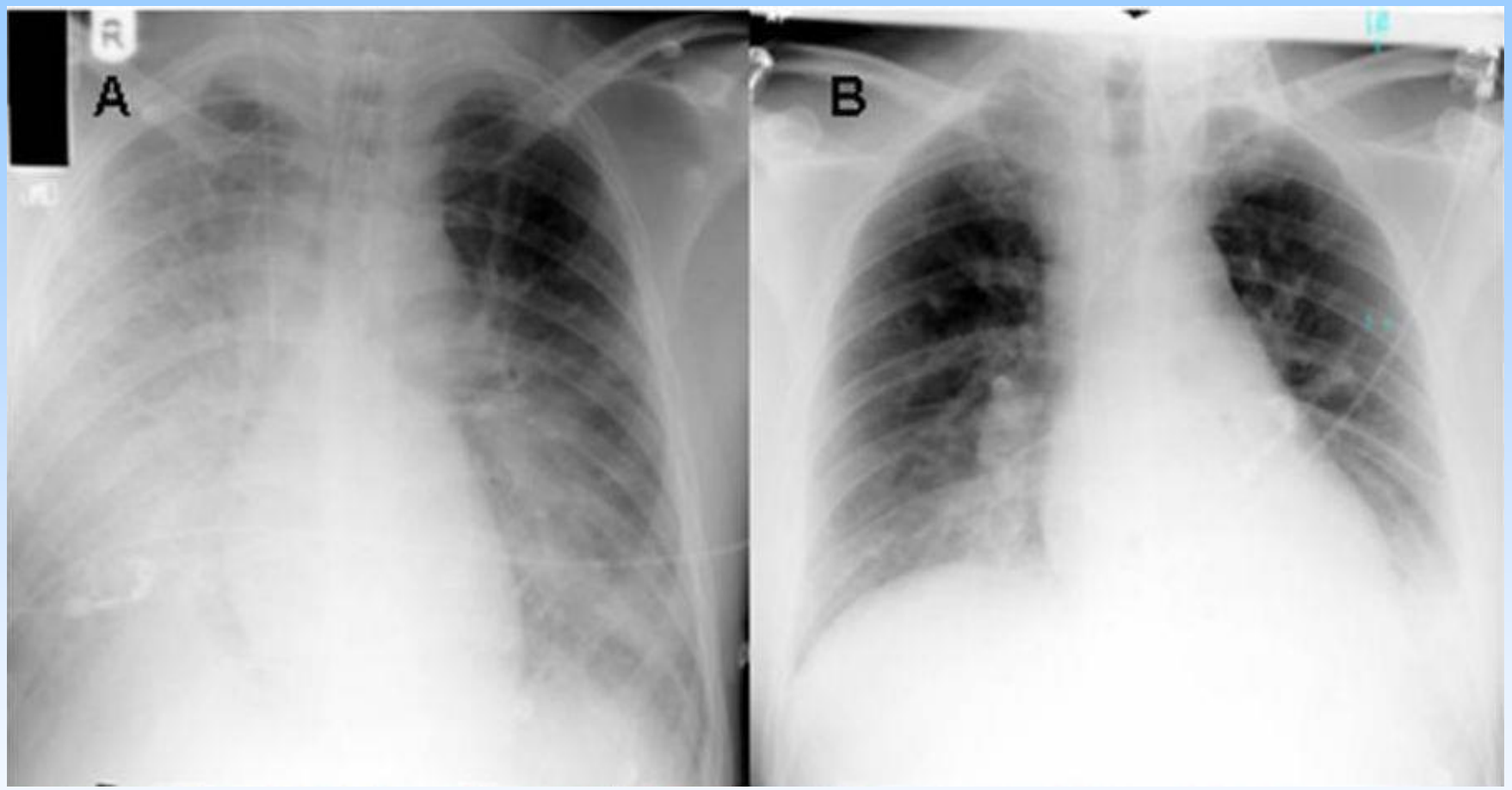


N Engl J Med 2006;355:1018-28

**Table 1. Data for All Six Affected Patients on Transfer to the Intensive Care Unit (ICU).***

| Characteristic | Patient No. | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Age (yr) | 24 | 34 | 31 | 19 | 28 | 20 |
| Weight (kg) | 68.9 | 84.3 | 81.8 | 72.1 | 88.5 | 82.4 |
| TGN1412 dose (mg) | 6.8 | 8.4 | 8.2 | 7.2 | 8.8 | 8.2 |
| Transfer to critical care (hr after dose) | 15.5 | 16.0 | 16.0 | 16.0 | 16.0 | 12.0 |
| APACHE II score on transfer† | 8 | 10 | 11 | 18 | 20 | 18 |
| Bilateral pulmonary infiltrates‡ | + | ++ | ++ | ++ | ++ | +++ |
| Duration of abnormalities on chest radiography (days) | 7 | 6 | 8 | >5 | 6 | 7 |
| Hemodynamics on transfer | | | | | | |
| Blood pressure (mm Hg) | 120/50 | 124/79 | 107/42 | 98/40 | 95/40 | 80/64 |
| Heart rate (beats/min) | 125 | 103 | 116 | 120 | 105 | 140 |
| LVEF on echocardiogram (%) | 50–55 | 70 | 60 | 50–55 | 60 | 55 |
| $PaO_2$:$FiO_2$ | 395.5 | 195.6 | 329.5 | 321.3 | 201.8§ | 84.0§ |
| Base deficit (mmol/liter) | −5.1 | −6.5 | −5.6 | −5.8 | −10.3 | −8.2 |
| Lactate (mmol/liter)¶ | 3.1 | 4.5 | 5.7 | 6.0 | 5.9 | 4.2 |
| Urinary output (ml/hr) | 20 | 30 | 30 | 45 | 30 | 0 |

P/F ratio **34.9** (11.2- 53.7) kPa

lactate **5.1** (3.1 to 6.0) mmol/L

base deficit **-6.2** (-5.1 to -10.3) mmol/L

N Engl J Med 2006;355:1018-28

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**Table 2.** Median Results of Blood Tests for the Six Patients before Infusion and 8 and 16 Hours after Infusion of TGN1412.*

| Blood Level of Constituent | Independent Clinical Trials Unit | | | Intensive Care Unit | |
|---|---|---|---|---|---|
| | Before Infusion | 8 Hours after Infusion | Normal Range | 16 Hours after Infusion | Normal Range |
| Creatinine (μmol/liter) | | | | | |
| Median | 80 | 128 | — | 163 | — |
| Range | 74–89 | 106–195 | 66–112 | 125–325 | 62–115 |
| Urea (mmol/liter) | | | | | |
| Median | 4.8 | 6.4 | — | 9.3 | — |
| Range | 3.6–6.0 | 6.1–7.6 | 1.7–8.3 | 7.3–7.7 | 3.2–7.4 |
| Prothrombin time (sec) | | | | | |
| Median | 11.2 | 14.2 | — | 26.2 | — |
| Range | 10.5–11.7 | 13.1–19.5 | 10.0–12.0 | 19.5–33.2 | 11.5–16.0 |
| Activated partial-thromboplastin time (sec) | | | | | |
| Median | NA | NA | — | 43.5 | — |
| Range | | | | 40.1–61.9 | 26.0–38.0 |
| Fibrinogen (g/liter) | | | | | |
| Median | NA | 1.47 | — | 1.69 | — |
| Range | | 0.66–1.75 | 1.50–4.00 | 0.99–1.98 | 2.00–4.50 |
| D-dimer (ng/ml) | | | | | |
| Median | NA | NA | — | 1784 | — |
| Range | | | | 1350–4535 | 0–250 |

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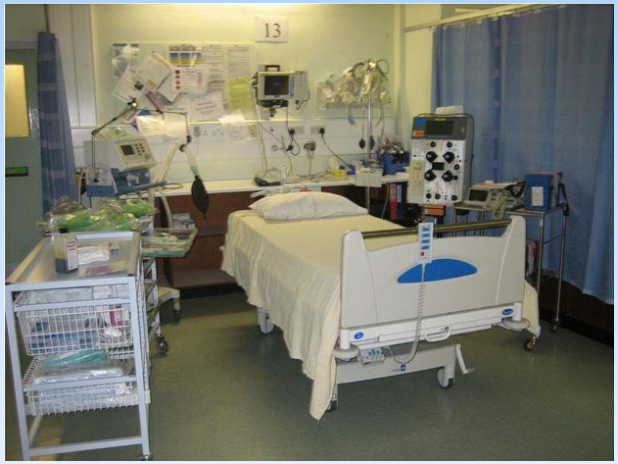
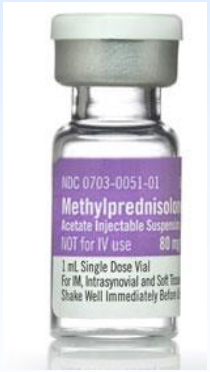
# By 12-16 hours

- Established
  - Pulmonary injury
  - Hemodynamic instability
  - Acute kidney injury
  - Coagulopathy
  - Lymphopenia & monocytopenia
  - Lactic acidosis



# Clinical management

- immune modulation
  - methylprednisolone 1g tds (→ tailing dose)
  - daclizumab (IL-2 receptor antagonist)
  - ranitidine, chlorpheniramine




# Clinical management

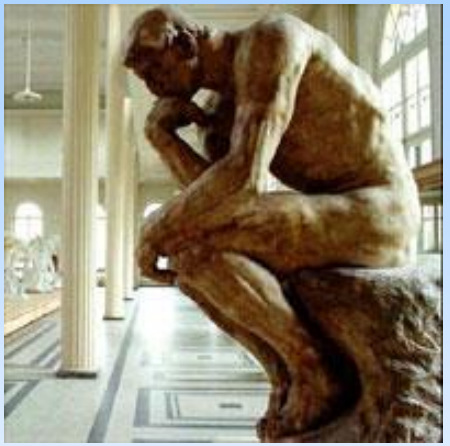
- organ support & management of SIRS
  - haemodynamic resuscitation
  - protective lung ventilation (2 pts), CPAP (4 pts)
  - high volume haemofiltration (6 pts)
  - tight glucose control (?valid)
  - rhAPC considered but rejected

# Key difficulties, decisions & ethics

- Unpredictable effects
- Unpredictable severity
- Unknown kinetics in humans

→

- Admit as a cohort?
- Treat as a cohort ?

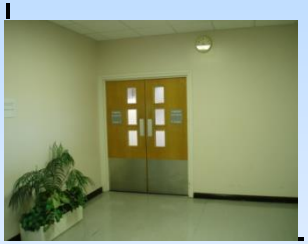


lab results

T + 8 hours

patient 6
MSOF

T + 10-12 hrs



patient 5
MSOF

T + 14 hrs

SIRS+organ
impairment,
all patients

T + 12-48 hours

ICU transfer,
organ support

Rx immune
modulation


recovery,
pts 1-4

T + 48 hrs →

MSOF,
pts 5-6

T + 9-16 days

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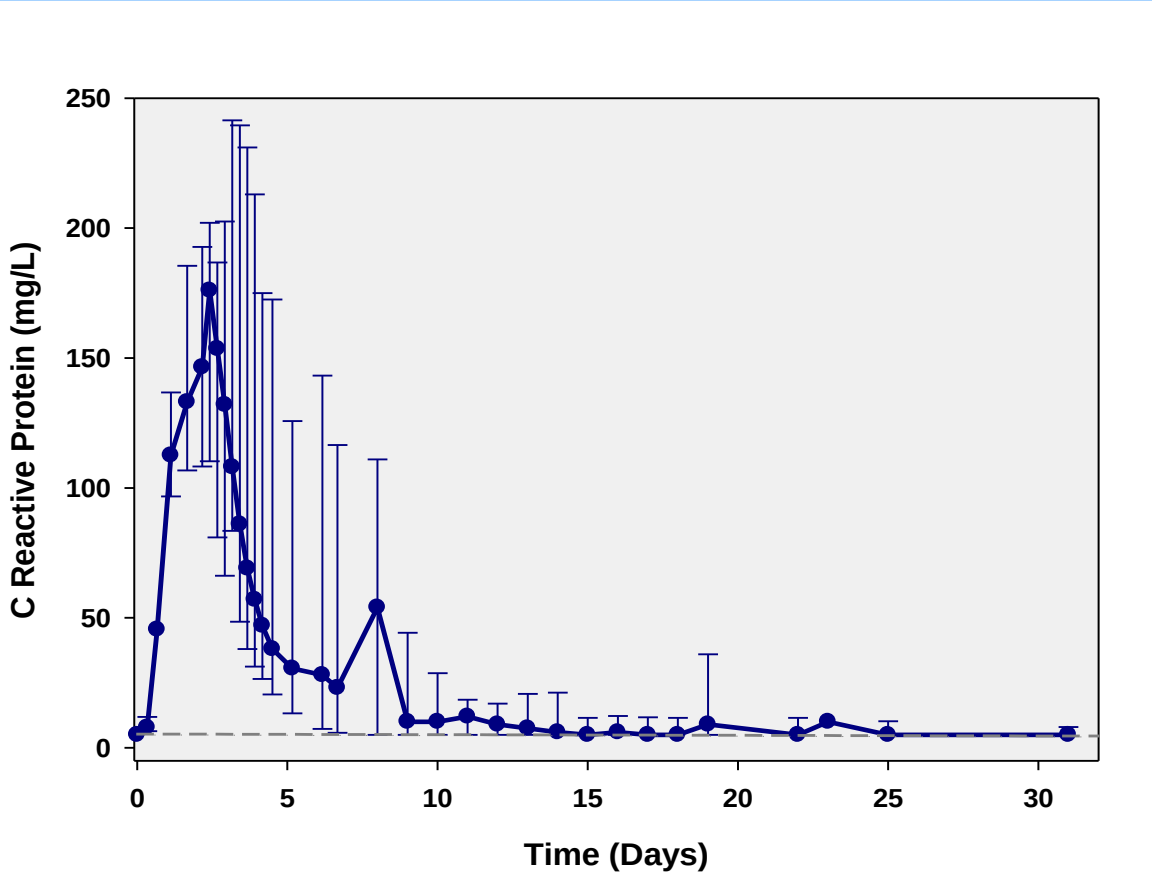
# CRP

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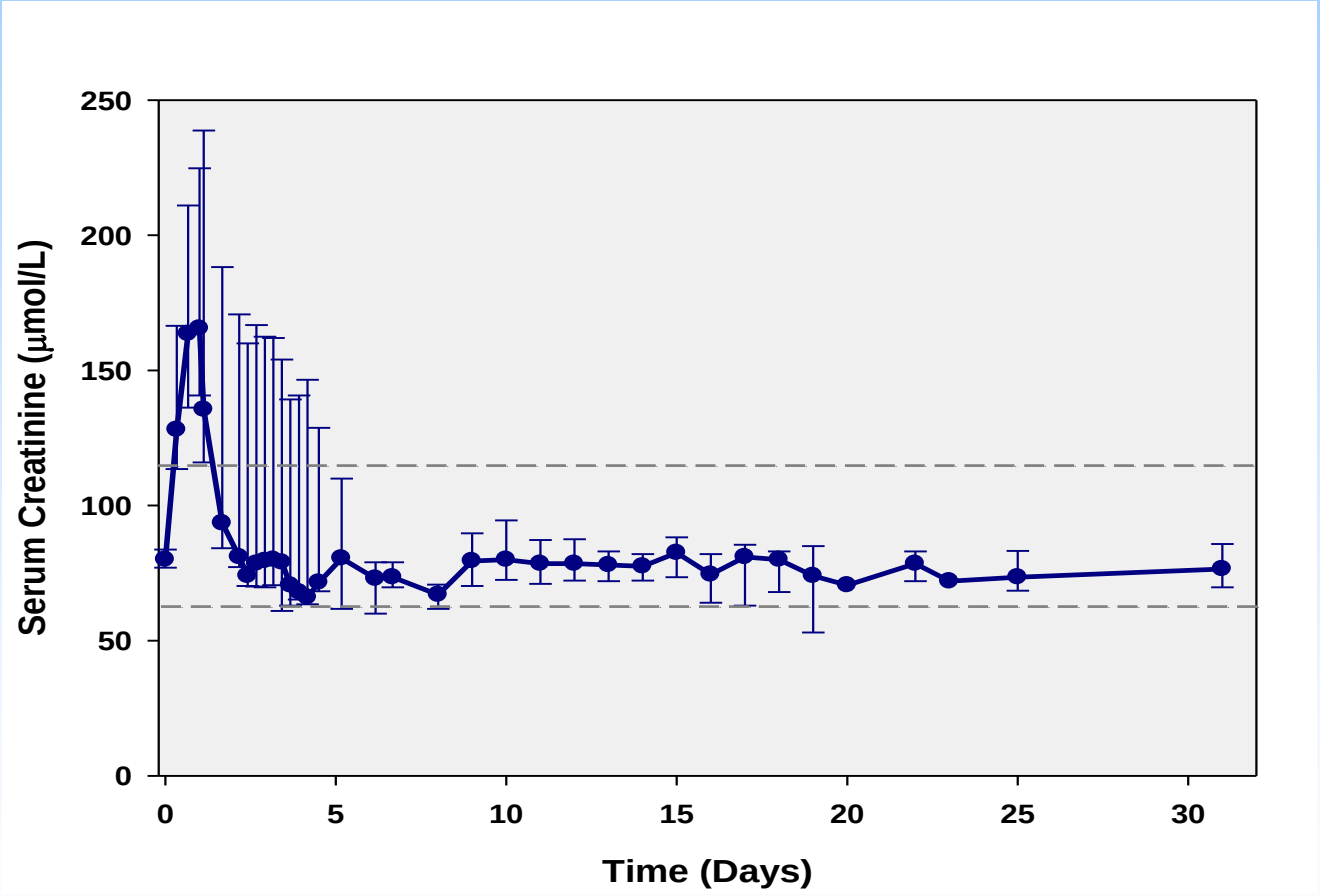
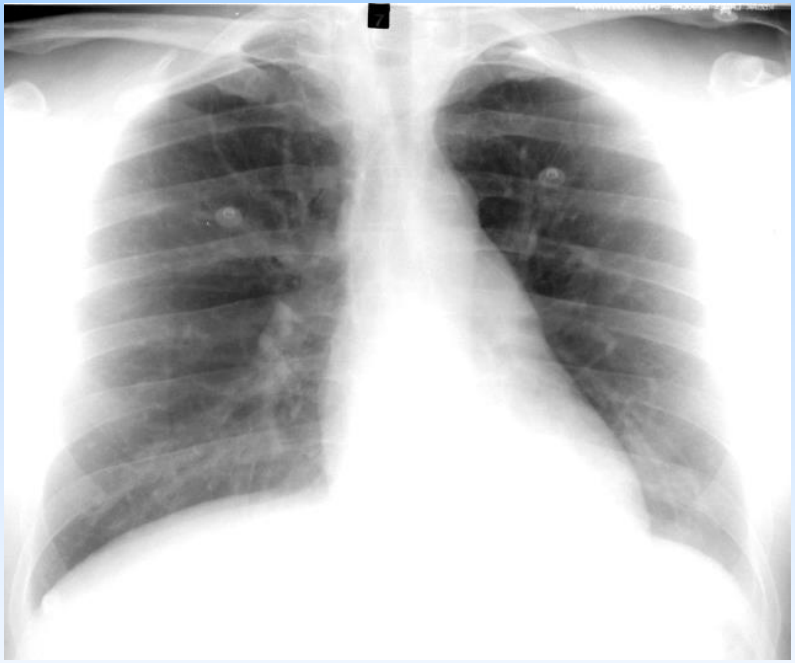
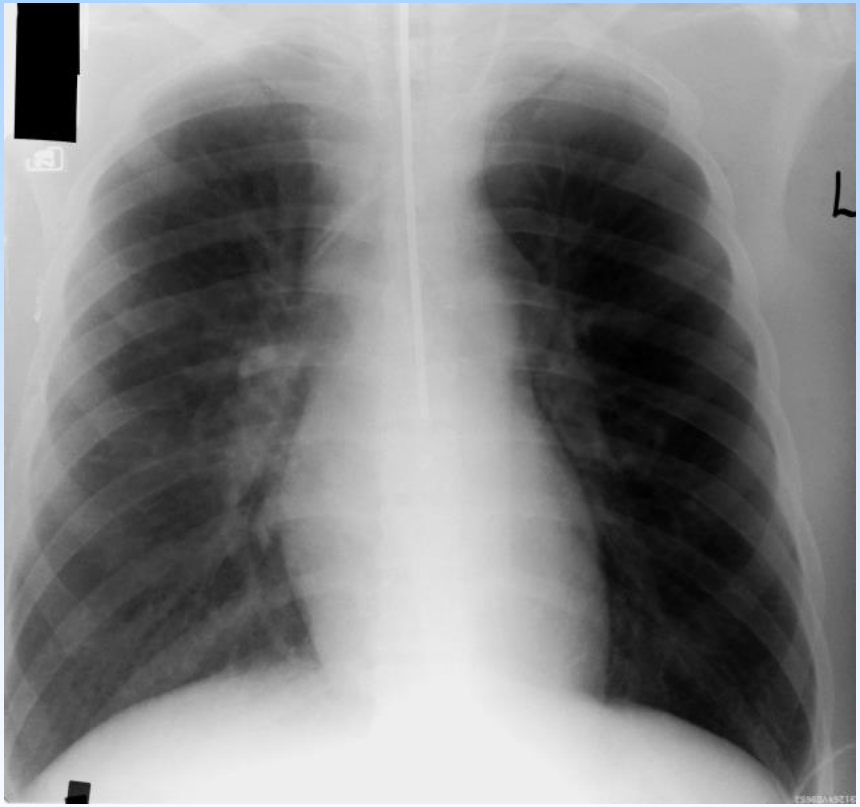
# Creatinine


Serum Creatinine (µmol/L)
250
200
150
100
50
0
0
5
10
15
20
25
30
Time (Days)

# Pulmonary resolution





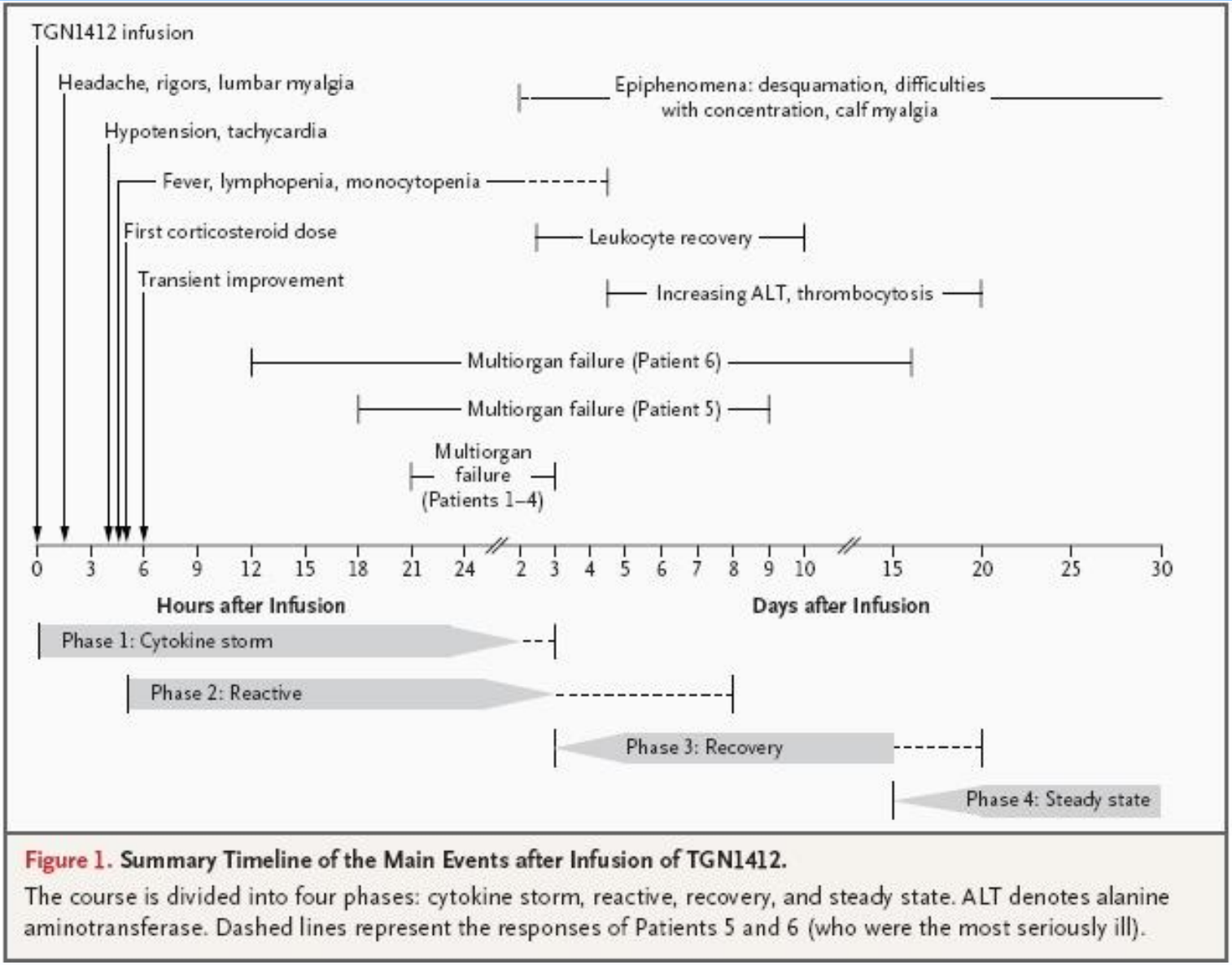



**Figure 1. Summary Timeline of the Main Events after Infusion of TGN1412.**

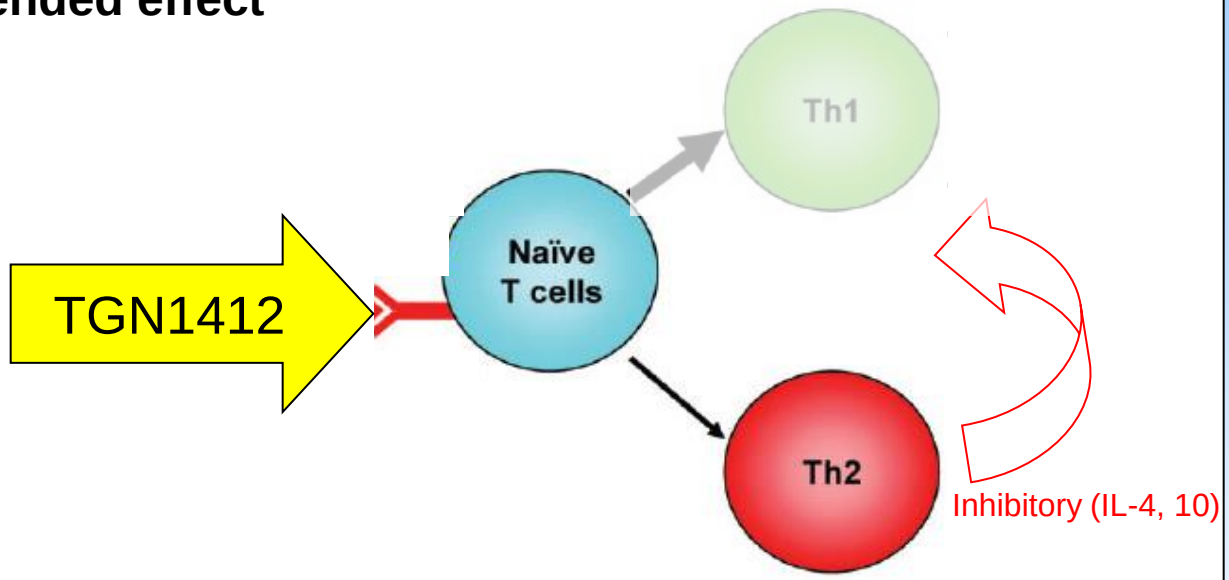
The course is divided into four phases: cytokine storm, reactive, recovery, and steady state. ALT denotes alanine aminotransferase. Dashed lines represent the responses of Patients 5 and 6 (who were the most seriously ill).

# Outcome

- All six patients survived
- Full resolution of pulmonary injury and renal failure
- 1 pt peripheral necrosis
- Prolonged haematological/ immunological recovery

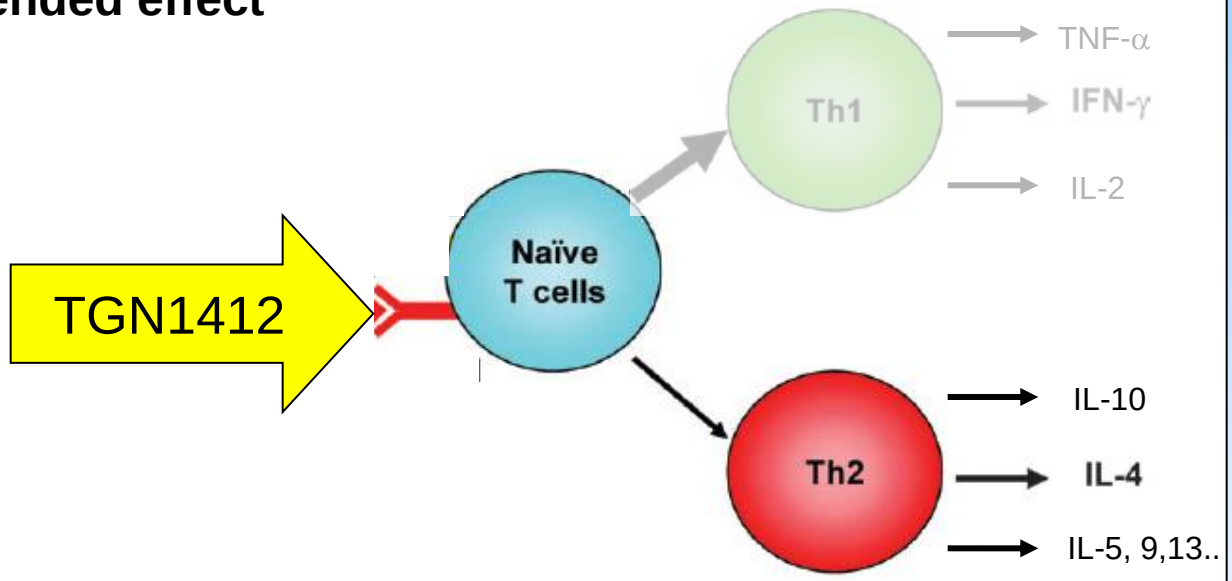
# What happened?

## Intended effect




*International Immunology, Vol. 17, No. 1, pp. 1–14*
doi:10.1093/intimm/dxh186

## Intended effect

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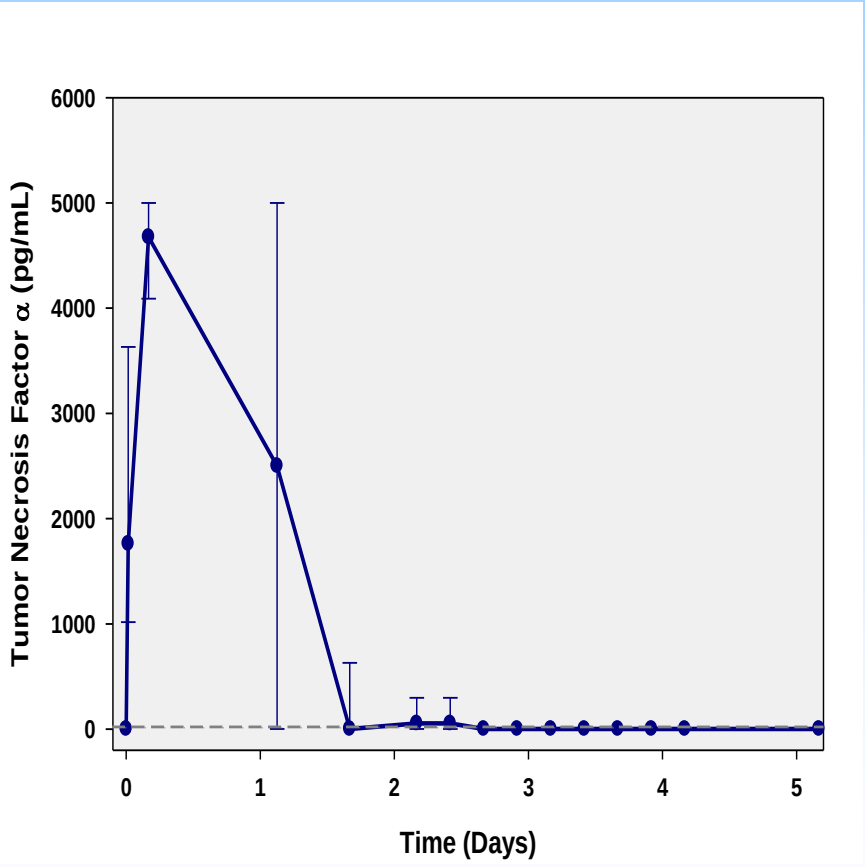
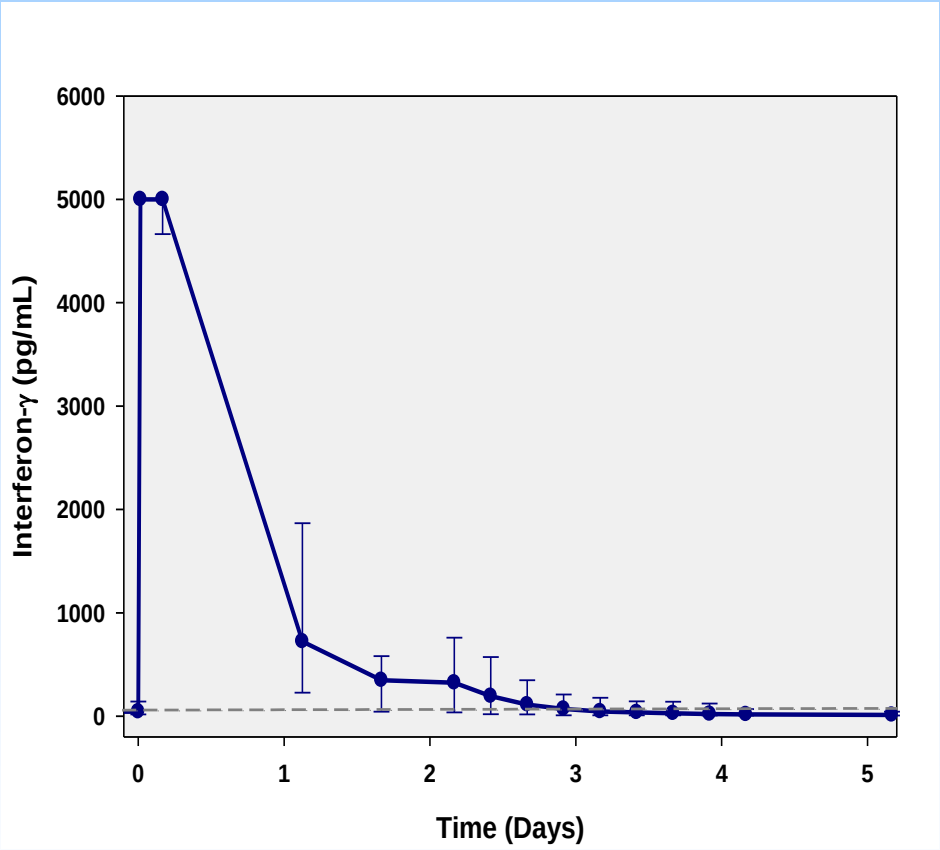
# TNF-α and IFN-γ

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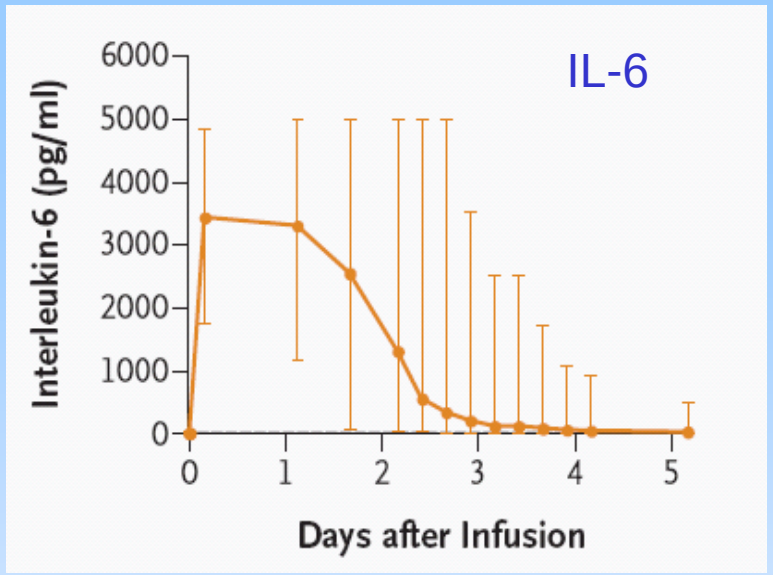
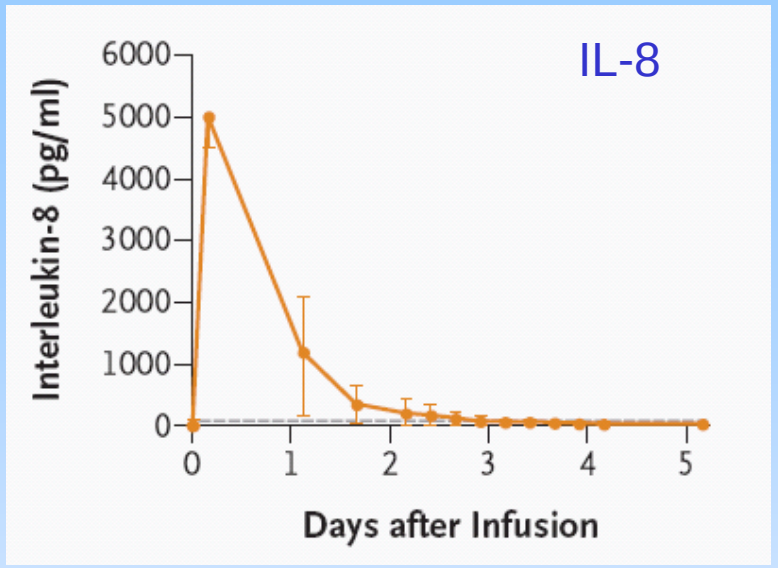
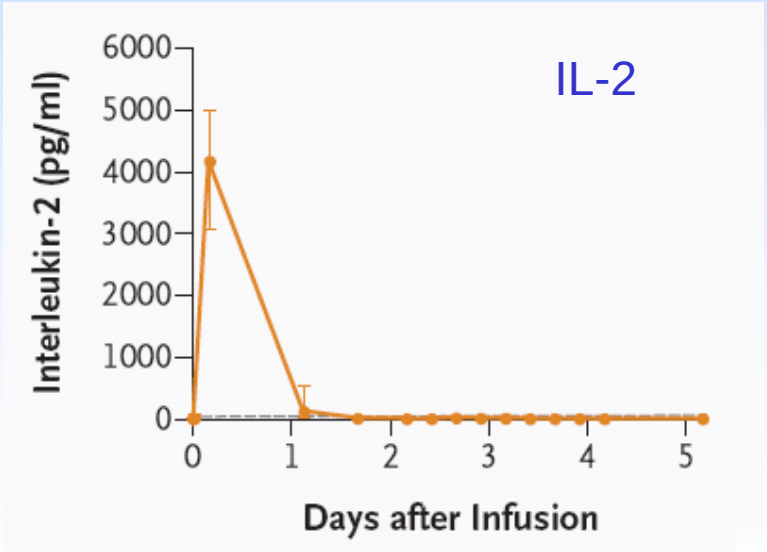
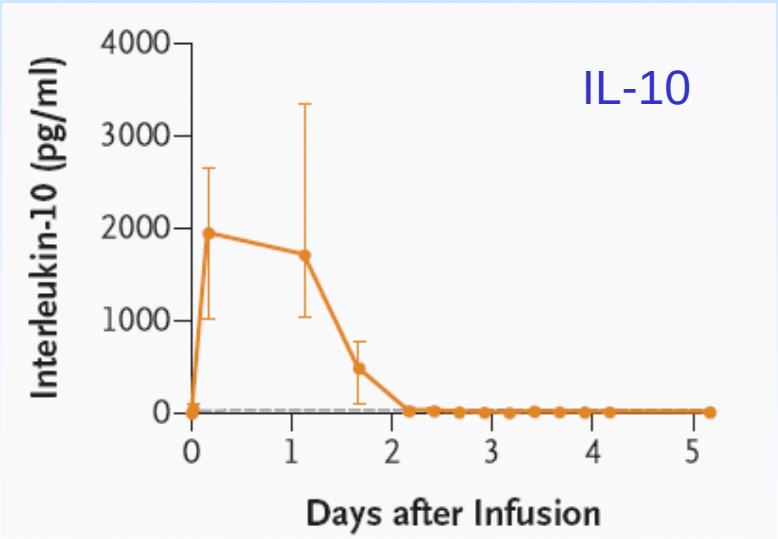


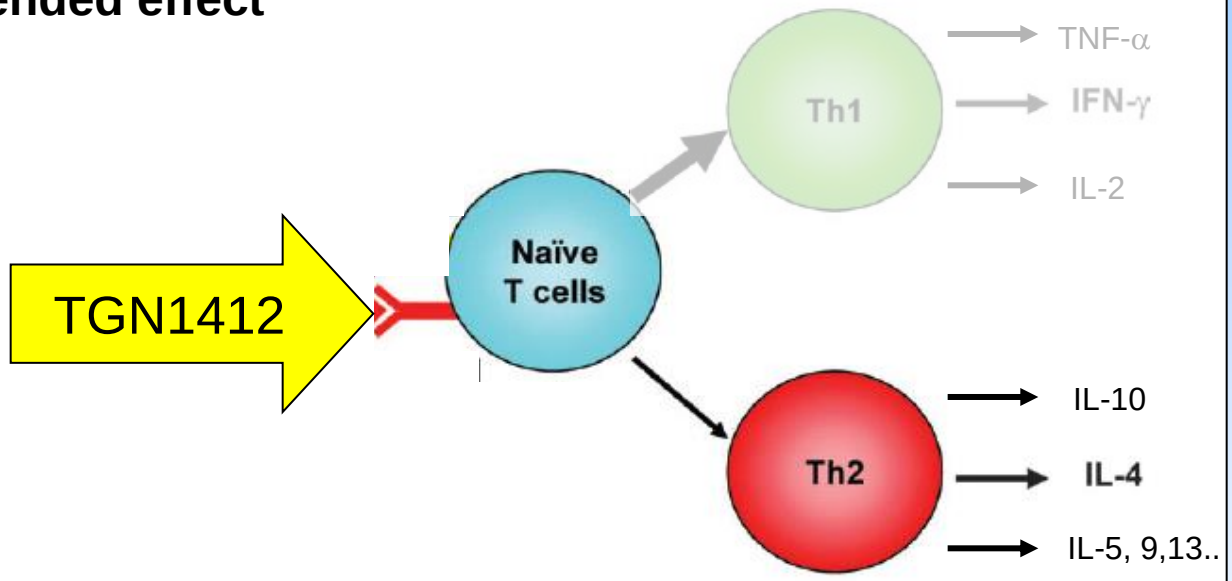




N Engl J Med 2006;355:1018-28.

## Intended effect

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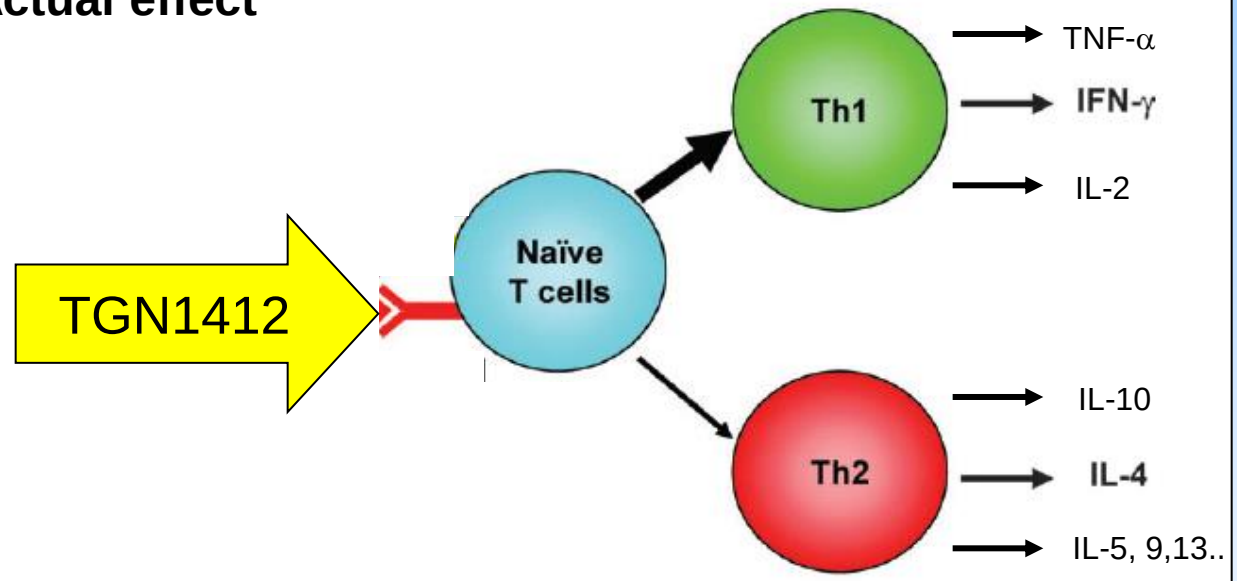
## ? Actual effect




*International Immunology, Vol. 17, No. 1, pp. 1–14*
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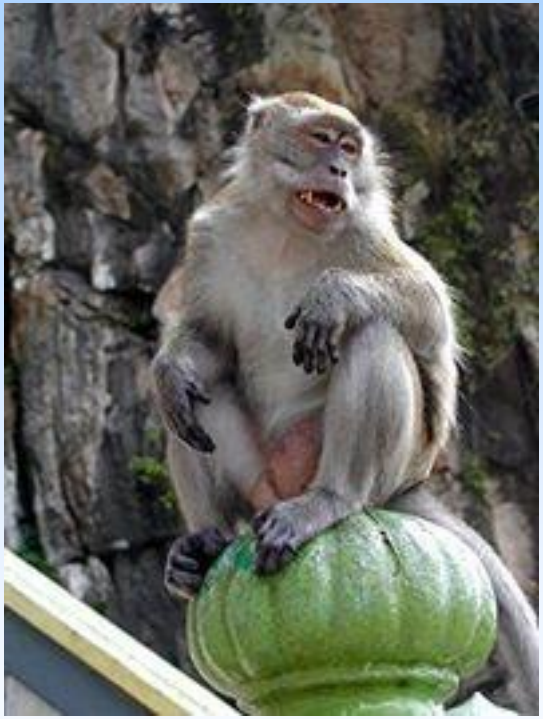
# Why different in humans?

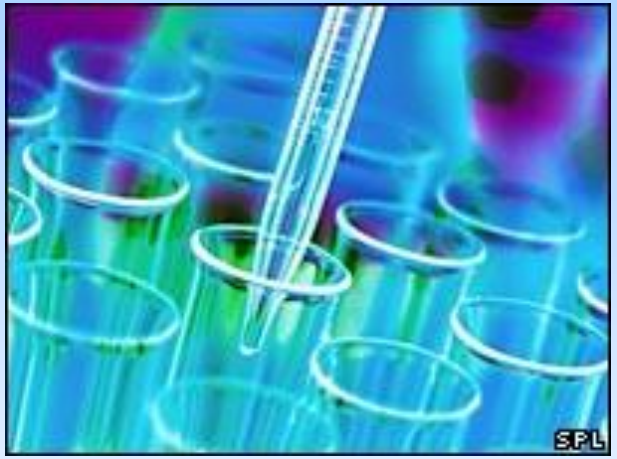
- Humanized antibody
- Naïve lab animals vs. real-world humans: memory cells
- Different molecular target in immune system



# Managing the incident

# Unusual aspects of TGN1412 incident

- ‘Chemical’ incident
- Internal incident
- Novel agent, empirical Rx
- Single-site story for media
- Immediate global consequences for trial conduct



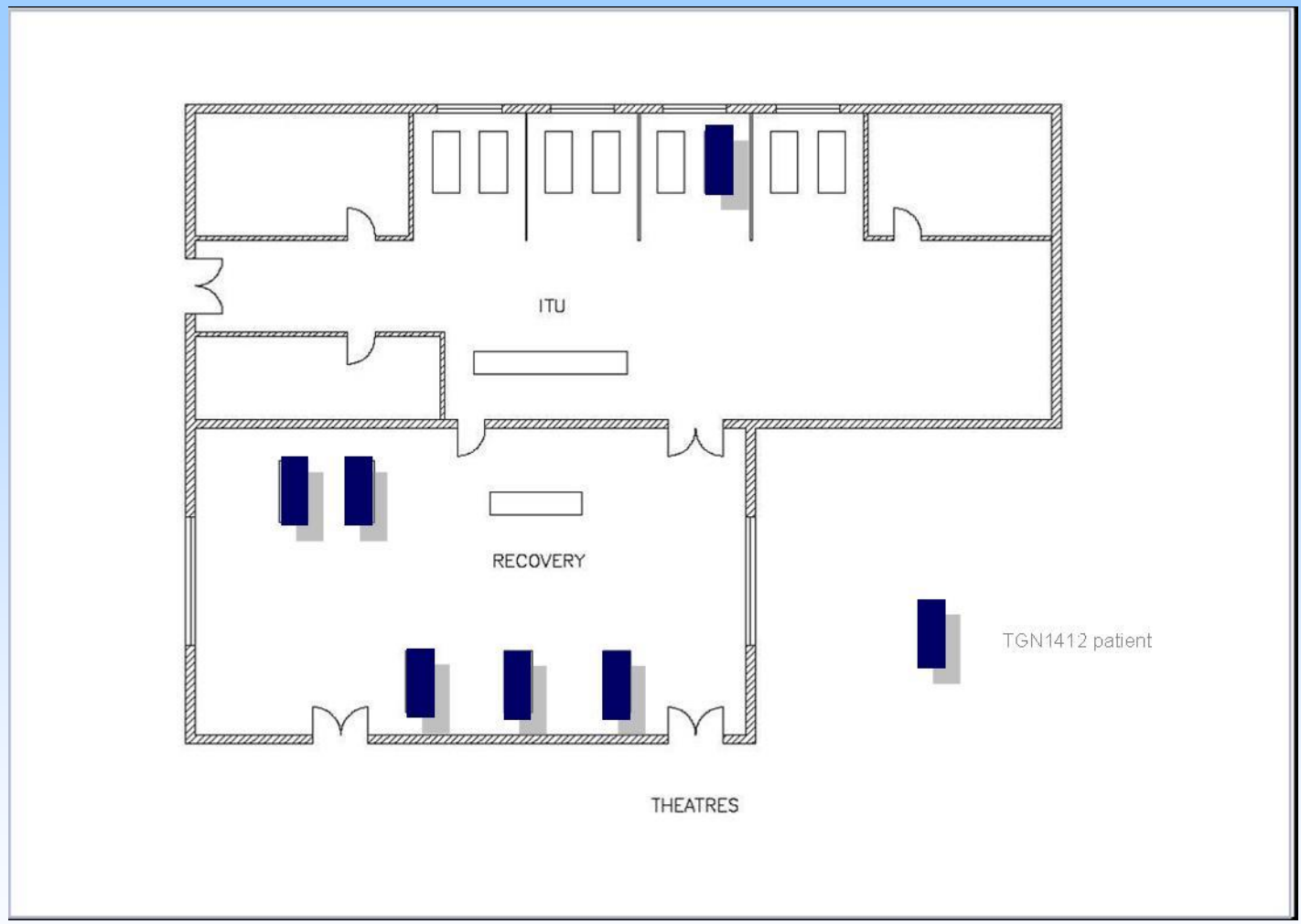
# However:

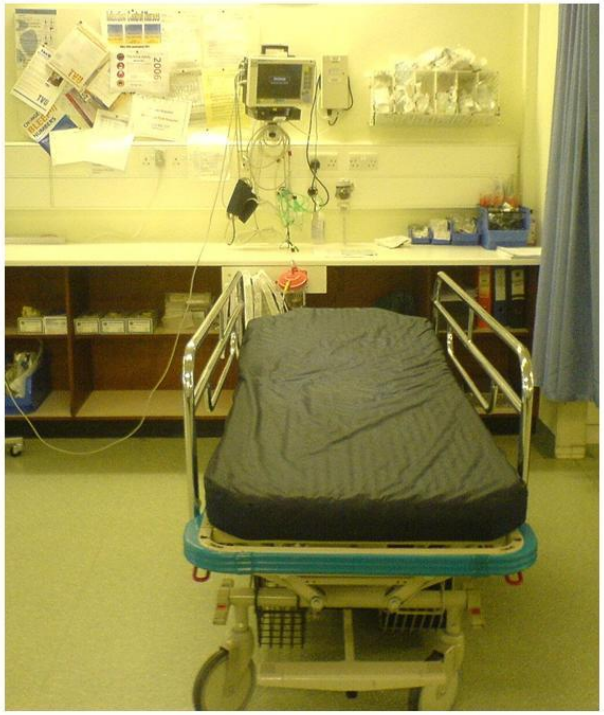
- No contamination issues
- No staff health issues
- Clear identification of agent

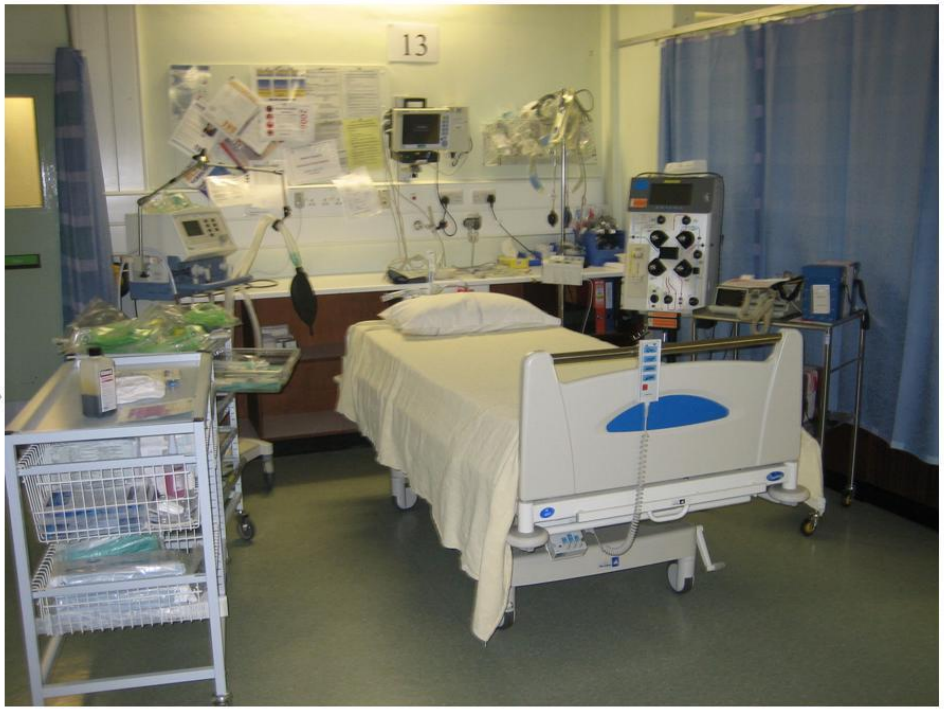
# Challenge 1 – physical capacity



- Space
- Staff
- Equipment


ITU
RECOVERY
TGN1412 patient
THEATRES

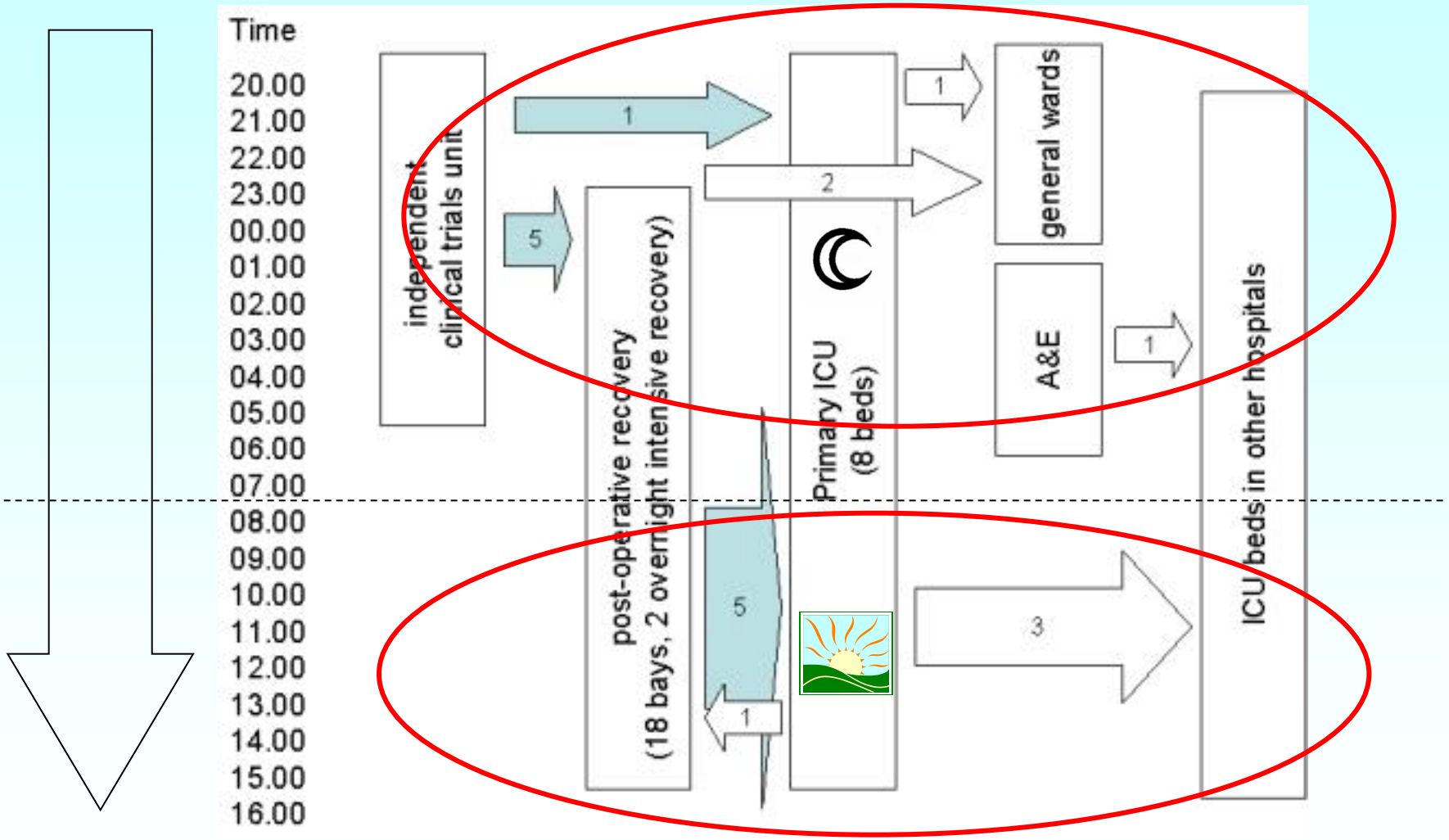


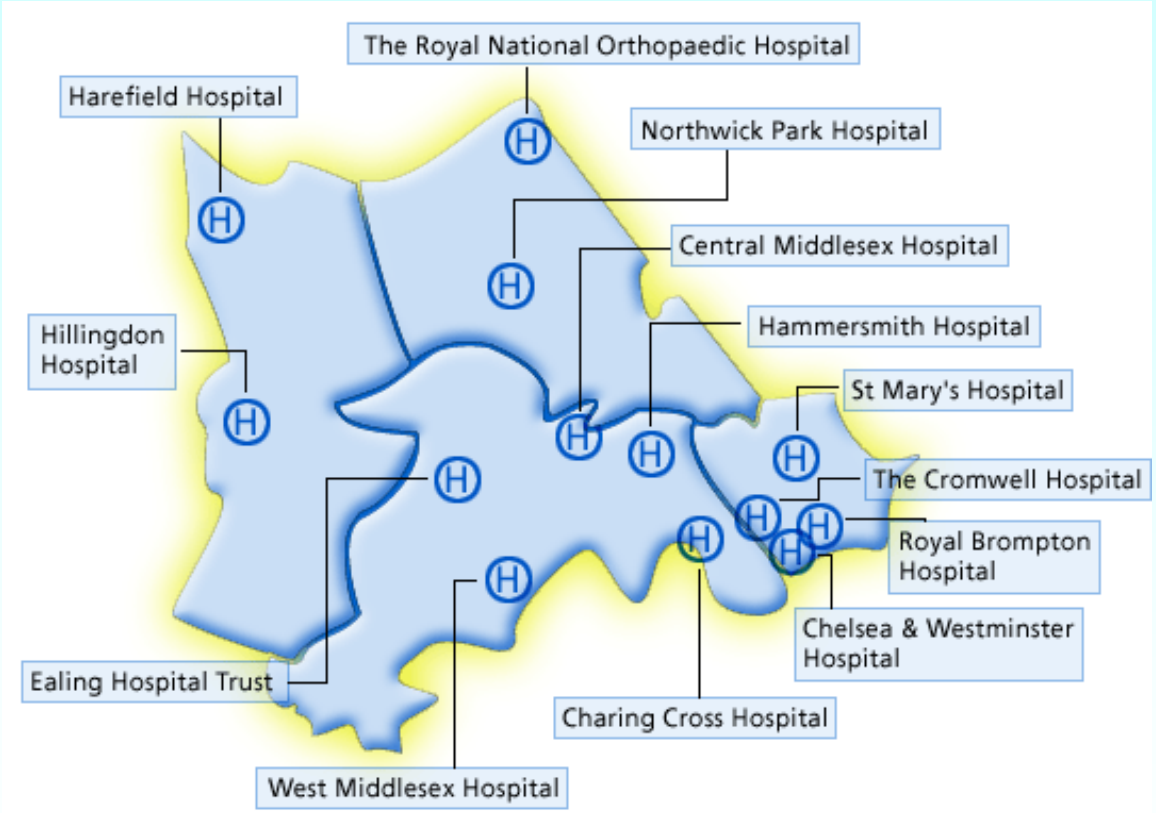

13

# Staffing strategy

- Staff:
  - ❖ Cross-skilled
  - ❖ ICU nursing ratio flexed
  - ❖ Assigned by role not patient
  - ❖ Deliberate decision to limit call-in
  - ❖ Sustainable numbers for 'the day after'

# Phasing of patient moves




The Royal National Orthopaedic Hospital
Harefield Hospital
Northwick Park Hospital
Central Middlesex Hospital
Hillingdon Hospital
Hammersmith Hospital
St Mary's Hospital
The Cromwell Hospital
Royal Brompton Hospital
Chelsea & Westminster Hospital
Ealing Hospital Trust
Charing Cross Hospital
West Middlesex Hospital

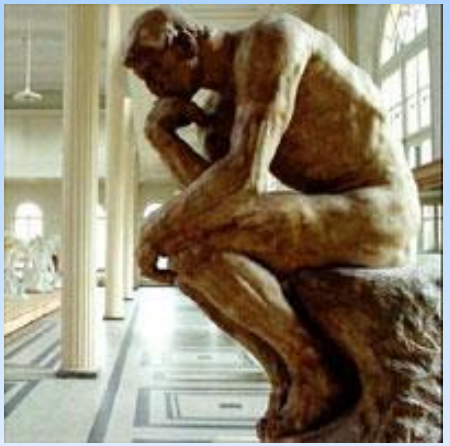
# Fate of moved (non-TGN1412) patients

| Patient | Location | Source of Referral | Admission Date | Diagnosis | Transfer Date | Transfer Destination | ITU Outcome | Hospital Outcome |
|---|---|---|---|---|---|---|---|---|
| A | HDU | Theatre | 13/03/2006 | Elective - for observation post Fem-distal bypass vein graft | 13/03/2006 | Ward - Internal | HDU - Survived | Survived |
| B | ITU | Ward | 20/02/2006 | Sepsis and Respiratory failure | 14/03/2006 | ITU - External | Survived | Survived |
| C | ITU | Theatre | 04/03/2006 | Sepsis and Respiratory failure | 13/03/2006 | Ward - Internal | Survived | Died |
| D | ITU | A&E - Internal | 07/03/2006 | Post Respiratory Arrest | 14/03/2006 | ITU - External | Survived | Survived |
| E | ITU | A&E - External | 12/03/2006 | Sodium Valproate Overdose | 14/03/2006 | ITU - External | Survived | Survived |
| F | A&E | A&E - Internal | 13/03/2006 | Status Epilepticus | 13/03/2006 | ITU - External | Survived | Survived |

Table 1. Outcomes of patients transferred in ICU mobilisation process

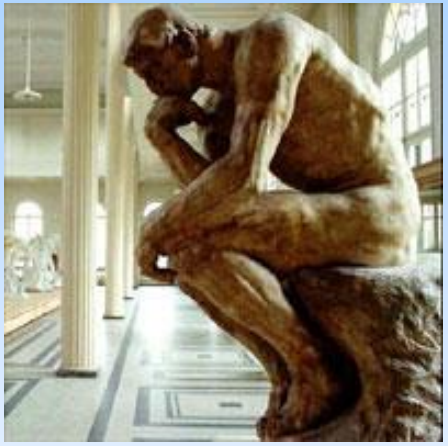
# Key physical capacity decisions

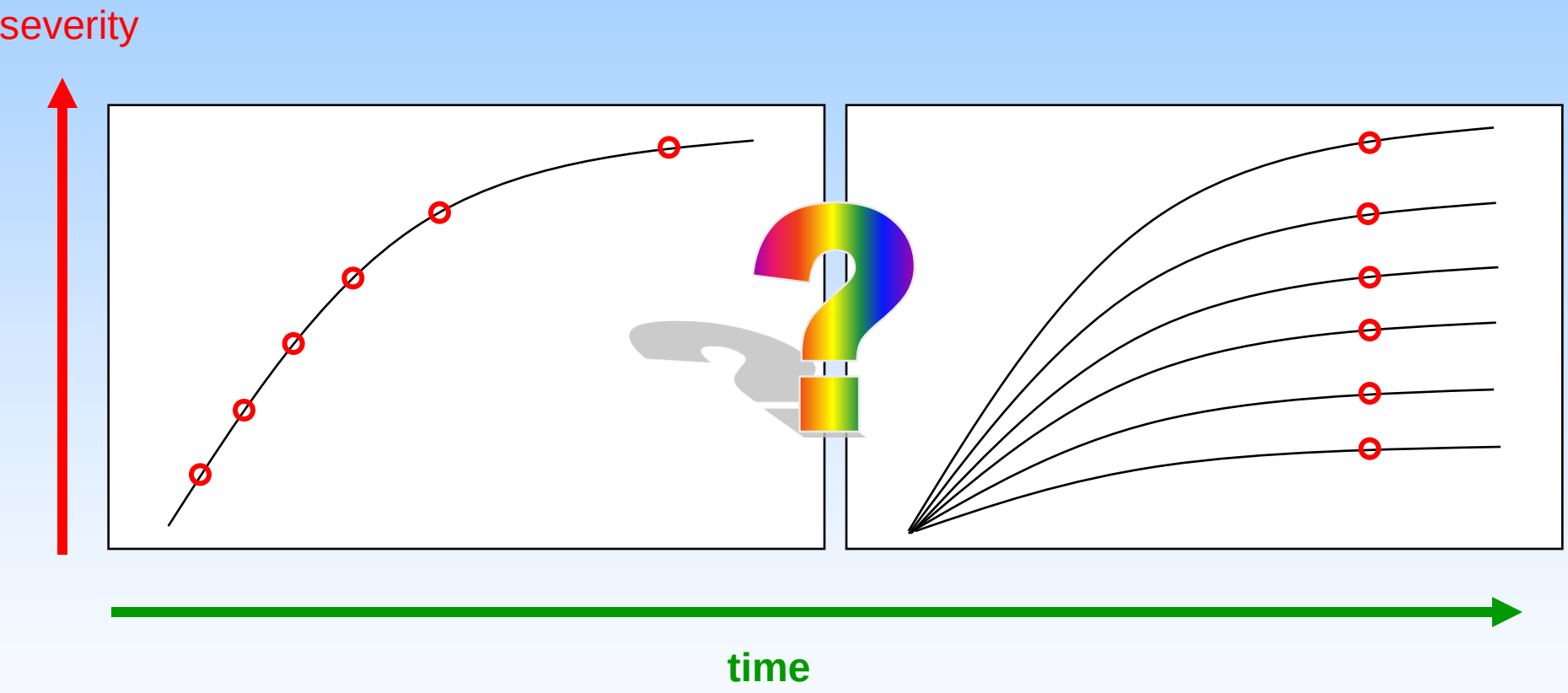
- Admit and treat as cohort
- Use of Recovery, limited call-in
- Phased evacuation of other ICU patients
- Deferred, major clinical team activation
- Continued elective theatre activity
- Activation of Trust management systems



# Challenge 2:
# Management of uncertainty

- Unpredictable effects
- Unpredictable severity
- Unknown kinetics in humans




severity
time

# Challenge 2:
# Management of uncertainty

- Unpredictable effects
- Unpredictable severity
- Unknown kinetics in humans

→

- Ethical issues:
- Admit as a cohort?
- Treat as a cohort ?
- Ethics of sampling (off-study)

# Challenge 3 – information management and decision-making

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NHS

# Challenge 3 – information management and decision-making

*Intensive Care Med. 2001 May;27(5):865-72*.

**The impact of organisational change on outcome in an intensive care unit in the United Kingdom**.

Baldock G, Foley P, Brett S.

*Crit Care Med. 2001 Apr;29(4):753-8*

**Intensive care unit physician staffing is associated with decreased length of stay, hospital cost, and complications after esophageal resection.**

Dimick JB, Pronovost PJ, Heitmiller RF, Lipsett PA

# Documentation

## (of all patients affected, including outward transfers)

# Challenge 4 - communications

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# Drug trial creates 'Elephant Man'

*(CNN, March 16, 2006)*

# Drug trial man's 'brain on fire'

(Sky News, March 16, 2006)

# Men seriously ill after experimental drug trial

(Guardian, March 16, 2006)

# 'Tighter controls needed to prevent UK drug trial fiasco'

(Times, March 16, 2006)

# Elephant Man drug trial horror'

(ABC News, March 16, 2006)

# ALL FINGERS AND TOES

(Daily Mail December 7, 2006)

(Mirror, June 26, 2006)

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# Particular media challenges

- Operational disruption
- Therapeutic rapport
  - Patient and family
- Confidentiality
  - Breaches of privacy
  - Patients identifiable in media
- Legitimate public interest
  - Accurate information vs. rumour
  - Implications for trial regulation

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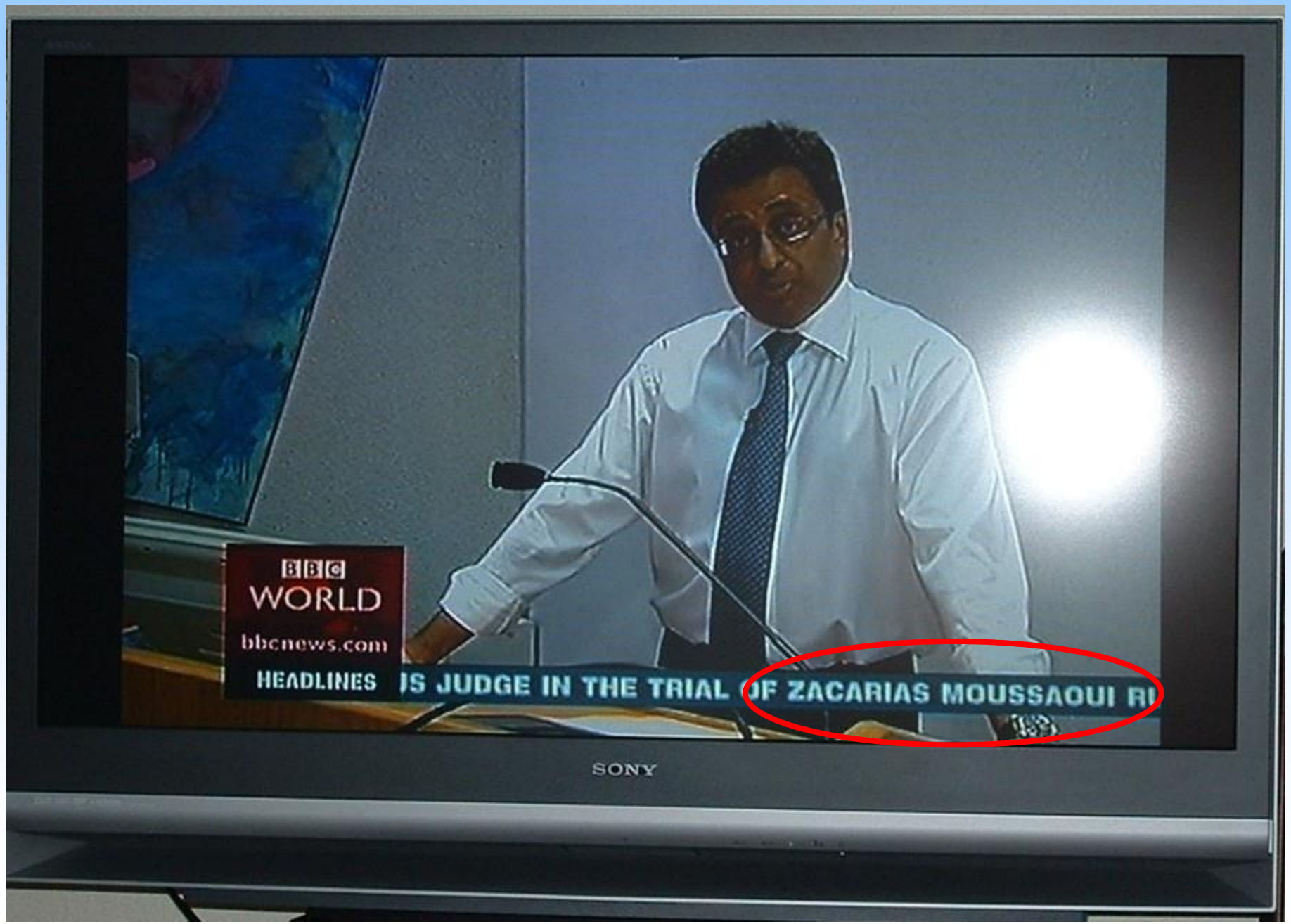
- Legitimate public interest
  - Accurate information vs. rumour
  - Implications for trial regulation

# Media strategy

- Press room
- Active regular accurate briefing
- “Credible source”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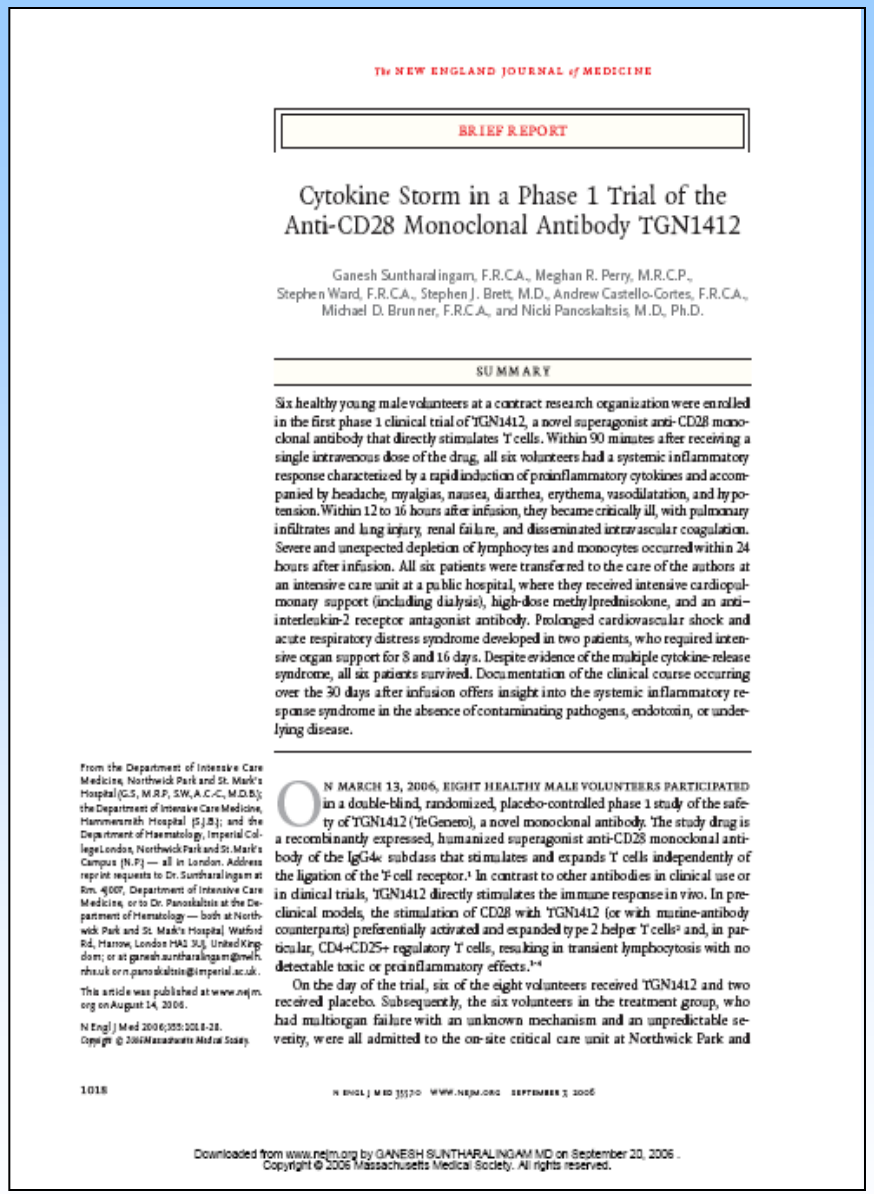
# Media strategy

- Press room
- Active regular accurate briefing
- “Credible source”
- Pooled interviews
- Control the message, keep confidentiality

# Challenge 5: disclosure, reporting

- ‘Duty to inform’
- Regulatory consequences
- Privacy
- Data ownership
- Intellectual property
- Defamation risk



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

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

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

SUMMARY

Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. Within 12 to 16 hours after infusion, they became critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Severe and unexpected depletion of lymphocytes and monocytes occurred within 24 hours after infusion. All six patients were transferred to the care of the authors at an intensive care unit at a public hospital, where they received intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti–interleukin-2 receptor antagonist antibody. Prolonged cardiovascular shock and acute respiratory distress syndrome developed in two patients, who required intensive organ support for 8 and 16 days. Despite evidence of the multiple cytokine-release syndrome, all six patients survived. Documentation of the clinical course occurring over the 30 days after infusion offers insight into the systemic inflammatory response syndrome in the absence of contaminating pathogens, endotoxin, or underlying disease.

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This article was published at www.nejm.org on August 14, 2006.

N Engl J Med 2006;355:1018-28.



ON MARCH 13, 2006, EIGHT HEALTHY MALE VOLUNTEERS PARTICIPATED in a double-blind, randomized, placebo-controlled phase 1 study of the safety of TGN1412 (TeGenero), a novel monoclonal antibody. The study drug is a recombinantly expressed, humanized superagonist anti-CD28 monoclonal antibody of the IgG4κ subclass that stimulates and expands T cells independently of the ligation of the T-cell receptor.[1] In contrast to other antibodies in clinical use or in clinical trials, TGN1412 directly stimulates the immune response in vivo. In preclinical models, the stimulation of CD28 with TGN1412 (or with murine-antibody counterparts) preferentially activated and expanded type 2 helper T cells[2] and, in particular, CD4+CD25+ regulatory T cells, resulting in transient lymphocytosis with no detectable toxic or proinflammatory effects.[3-6]

On the day of the trial, six of the eight volunteers received TGN1412 and two received placebo. Subsequently, the six volunteers in the treatment group, who had multiorgan failure with an unknown mechanism and an unpredictable severity, were all admitted to the on-site critical care unit at Northwick Park and





Imperial College London

The North West London Hospitals NHS Trust

# Aftermath

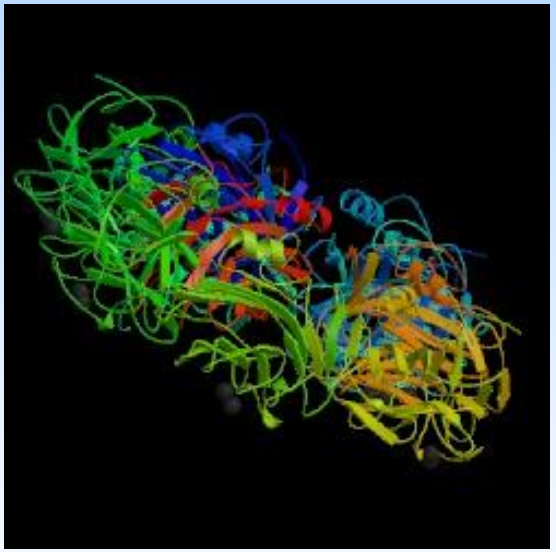
- Legal/complaints
  - TGN1412 patients
  - patients who were moved


- Regulatory
  - MHRA
  - Expert Scientific Group on Phase 1 Trials
  - Royal Statistical Society
  - EMEA, ABPI

# Biological/biotech agents

Adverse effect profiles of new chemical entities (NCE) vs novel biologics

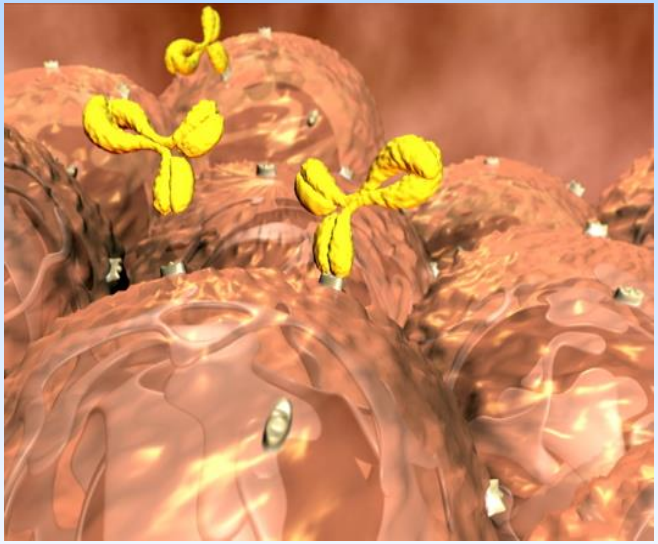
| | NCE | Biologics |
|---|---|---|
| Molecule size | small | large |
| Organ effects | Off-target | On-target |



# Biological/biotech agents

MHRA phase 1 trial approvals since Sept 2004

| | Patients | Healthy volunteers |
|---|---|---|
| Chemical | 82 | 842 |
| Biological/ biotech | 26 | 66 |



Hoffmann-La Roche Ltd., Basel, Switzerland

# Contract Research – growth area

# Key points

- Recognition of an evolving situation as a major incident
- Unusual aspects – novel agent, internal incident, complex scientific, ethical, clinical issues
- Huge external interest (academic, regulatory, governmental, commercial)
- Deviations from normal practice: task-based nursing, stable patients transferred, triumvirate on-call, expert panel
- “The incident worked because the Unit works” (ITU-Recovery); aided by good neighbours/Network

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## Drugs trial men 'are improving'

**Six men left seriously ill by a drugs tria some sig doctors s**

Two of the been take while anot less organ fully consc said.

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## Drugs trial pair out of hospital

**Two o seriou in a dr allowe**

Doctor Hospit said th well to made

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## Two more drug trial men sent home

**Two more men have been allowed home from hospital, two weeks after collapsing in pain during a clinical drugs trial in north-west London.**

Six men suffered agonising spasms shortly after being injected at a research unit on 13 March.

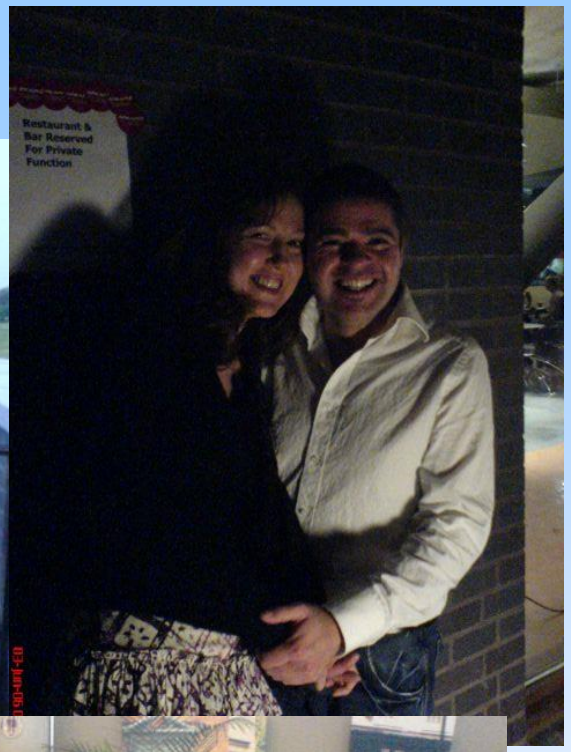
Two men are still being treated at Northwick Park hospital

They had had an inflammatory response to the drug TGN1412.

Imperial College London

The North West London Hospitals NHS Trust


STELLA ARTOIS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