Mid-recruitment trial redesign to incorporate genetic sub-types: the PICCOLO Trial

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On behalf of the PICCOLO Trial Team

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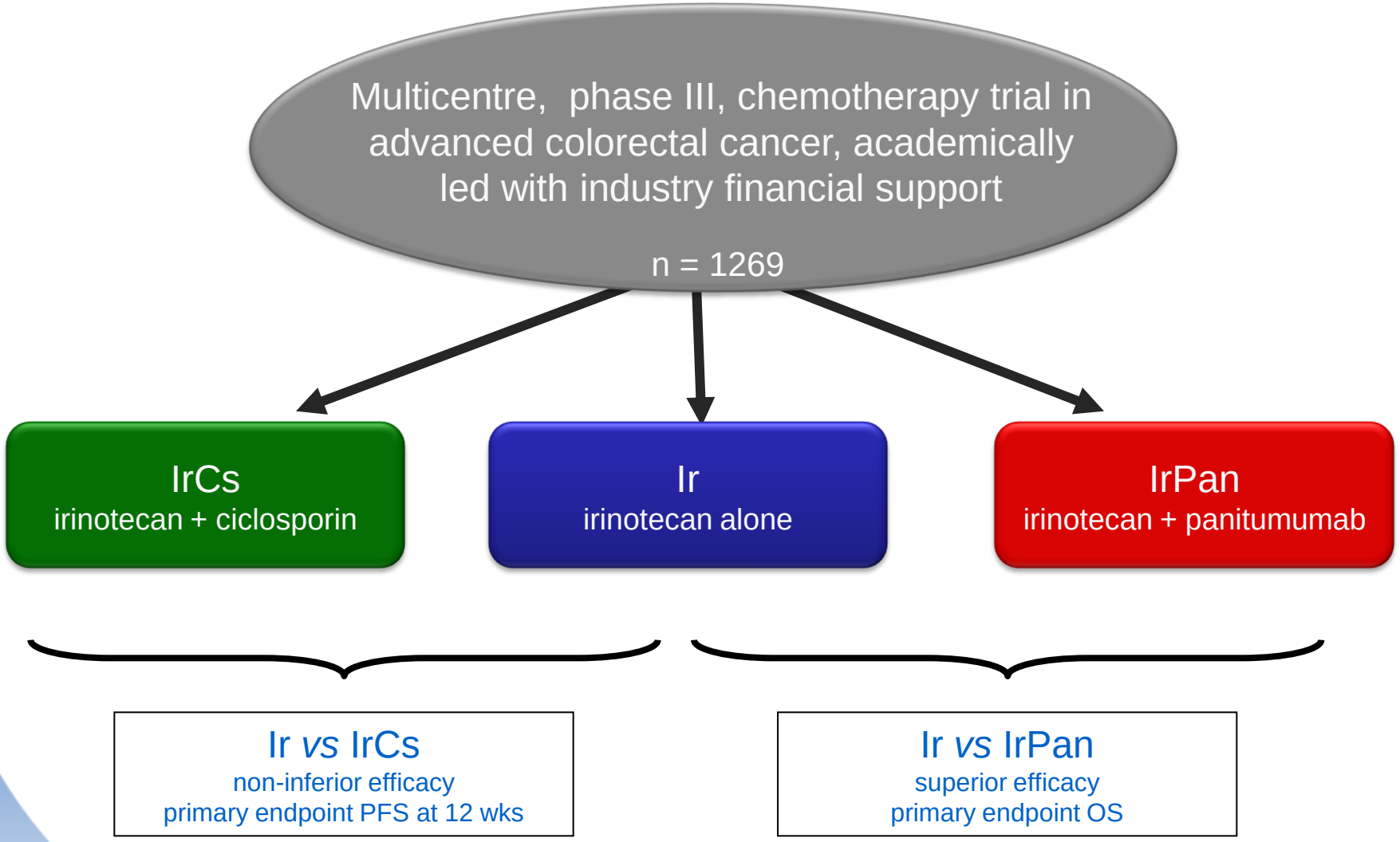
Overview

- PICCOLO was originally designed in 2006 however after new molecular data emerged in 2008 a redesign was necessary

- This new data presented a number of challenges -

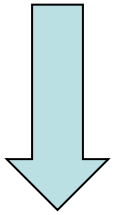
  - Urgent Safety Measure
  - Trial Redesign
  - Protocol Amendment
  - Acceptance and implementation of new design at trial sites
  - Implementation at CTRU
  - Initiation of prospective molecular testing service

PICCOLO Original Trial Design



New Molecular Data

- Data released at the ASCO meeting in Chicago (30 May - 03 June 2008)
- Showed beyond reasonable doubt that patients with *K-RAS* mutated colorectal cancer do not benefit from the addition of anti-EGFR monoclonal antibodies (cetuximab or panitumumab) to their chemotherapy.



Consequences for PICCOLO

Only patients with a *K-RAS* wild-type tumour receiving irinotecan plus panitumumab (IrPan) stand to benefit.

How did we react?

30th May – 3rd June	• American Society for Clinical Oncology Conference
4th June	• CI returns from ASCO. Internal discussion with TMG
9th June	• DMEC agrees to Urgent Safety Measure and new protocol design • 24hour automated randomisation service suspended
10th June	• Urgent safety measure implemented

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What is an Urgent Safety Measure?

- Regulation 30. in the The Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006)

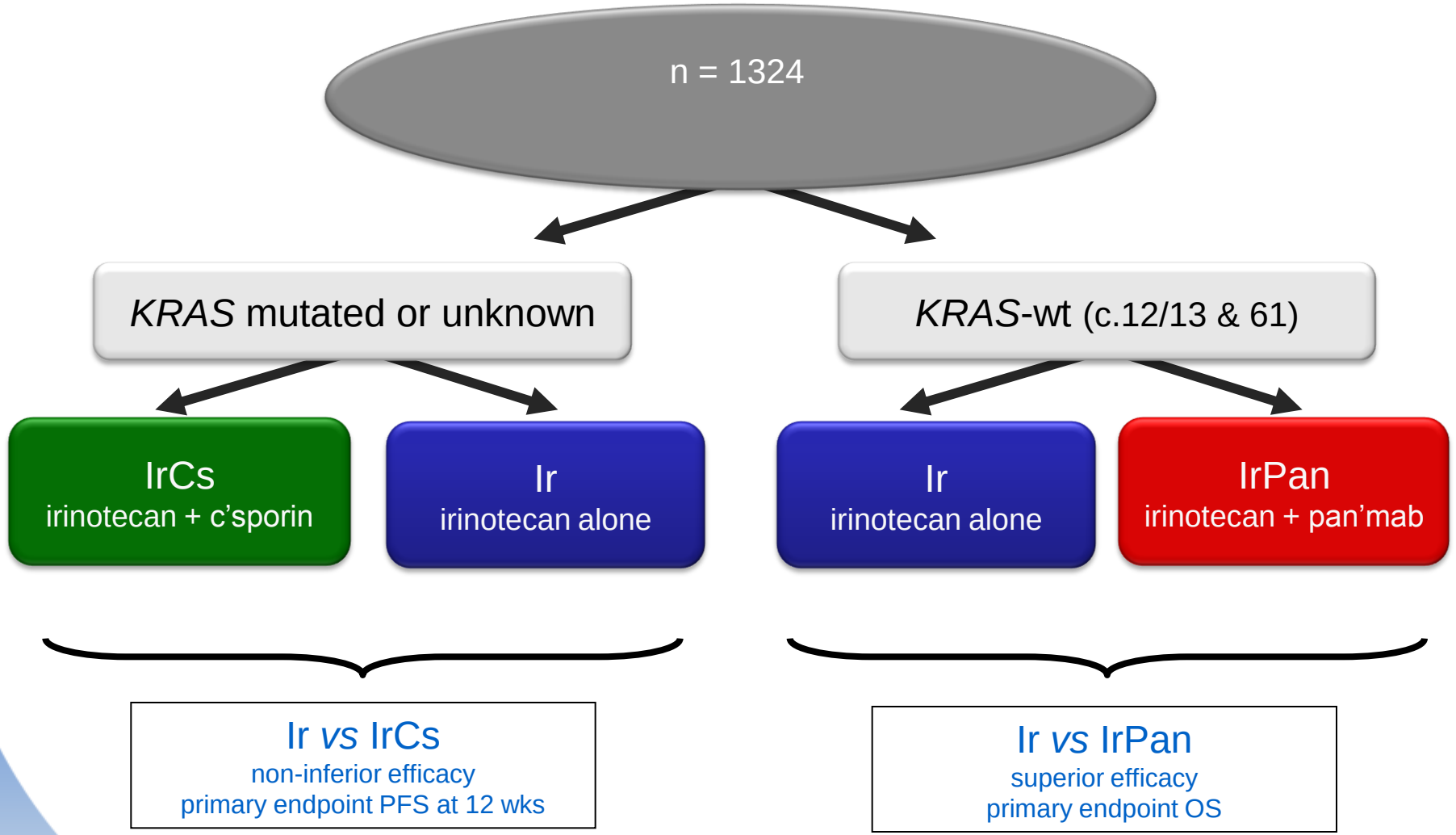
  - (1) The sponsor and investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety.

  - (2) If measures are taken pursuant to paragraph (1), the sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

Urgent Safety Measure

- Office hours (9am – 5pm) telephone paper randomisation implemented
- Allowed only patients with known *KRAS*- wt to be randomised to IrPan
- No action thought to be necessary for patients with *KRAS* mutant tumours already receiving Pan (Pan shown to have no benefit in these patients rather than cause harm)
- All trial sites urgently notified of changes

Trial Re-design



Protocol Amendment

Action:	Challenge:
• Substantial amendment to protocol and PIS	• Day-to-day trial management still needed
• KRAS specific consent required • New registration process prior to randomisation	• New system required additional testing
• TMG review & approval • Protocol implemented from October2008	• Time pressures

IMPACT: More man-power needed

Implementation of new design at trial sites

Action:

- Acceptance of new design
- Local approvals
- Keep centres informed /training

Challenge:

- Not all study sites liked the new trial design (in particular not releasing *KRAS* status)
- Concern re delaying tmt
- Can be a lengthy process
- Teething problems with new protocol and *KRAS* testing

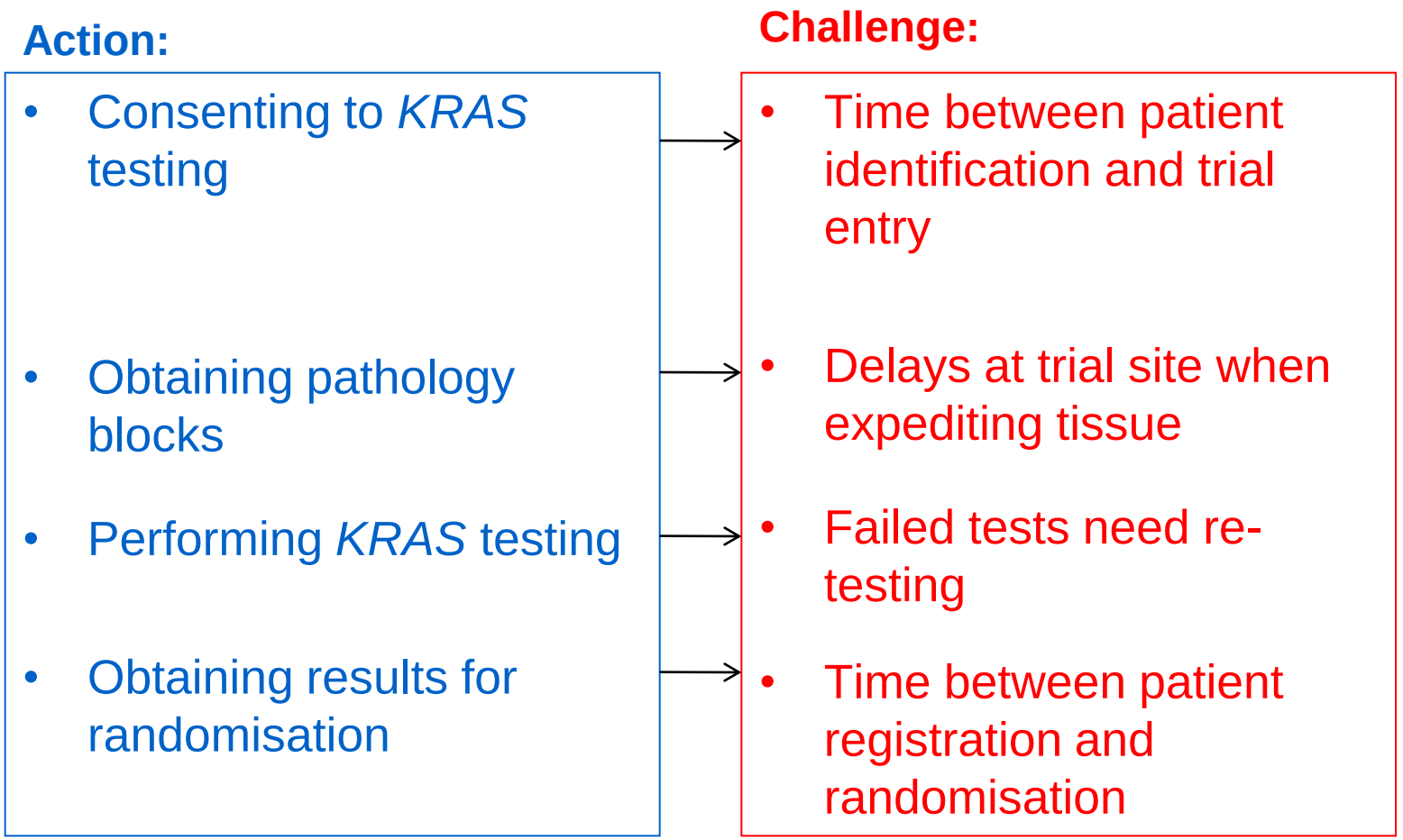
IMPACT: Knock on effect on recruitment

Implementation at CTRU

Action:	Challenge:
• Changes to CRFs to capture new data	• Knock on effect on database – consider data collected for patients under original protocol
• New administrative systems for central *KRAS* testing	• Test, implement and maintain new system
• Change to randomisation system including registration	• Ongoing queries from sites re KRAS status

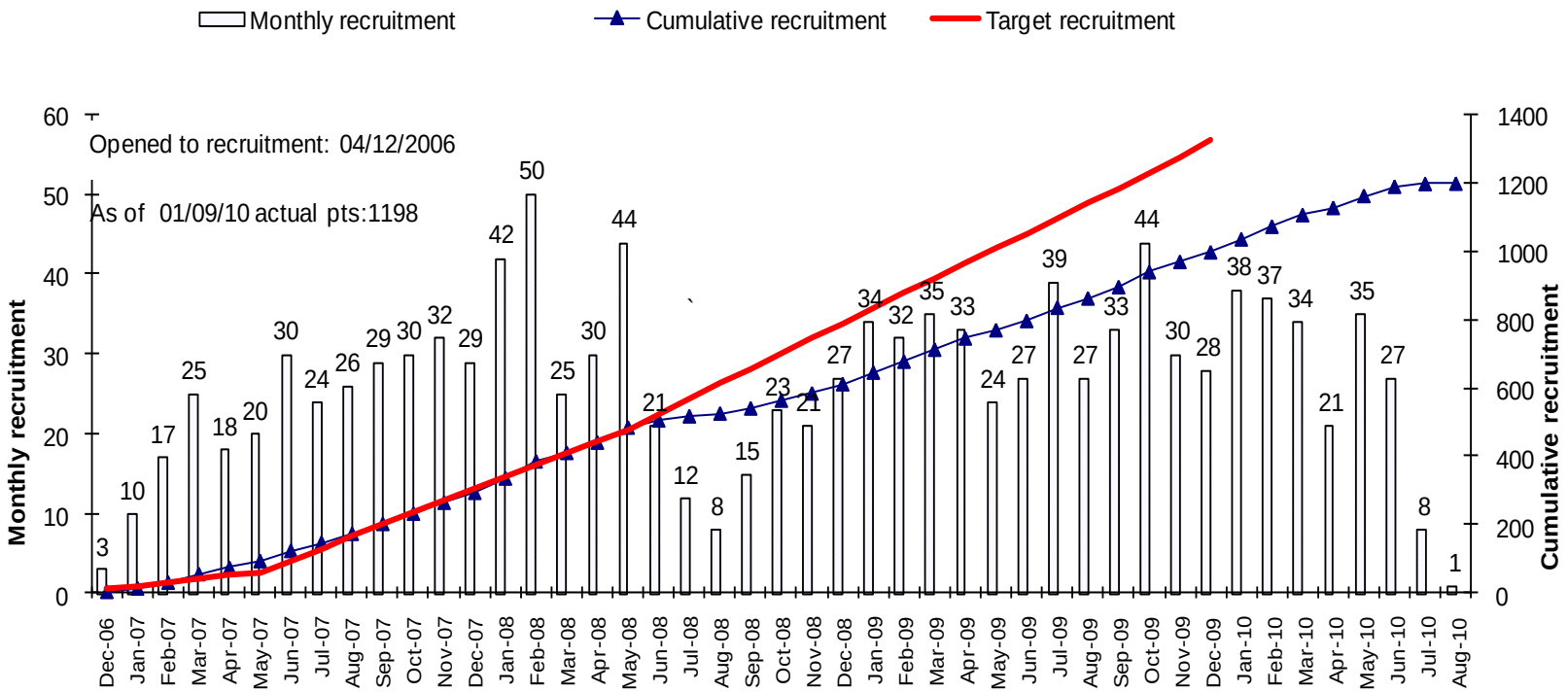
IMPACT: Day-to-day management of trial – man-power

Initiation of prospective molecular testing service



IMPACT: Day-to-day management of trial
Increased communication with sites & central lab

Effect on recruitment



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- New sites initiated and opened
- Negotiated extension with pharma partner and with CTAAC
- Continuous updates via trial newsletters

Points for Consideration

- Trials requiring a mid-recruitment redesign may become more common as further genetic advances are made
- Consider prospectively requesting consent for tumour collection
- Be realistic about manpower required for protocol writing and designing new systems – will affect regular trial activities
- Give ample training in new design, to ALL departments involved
- Minimise time between registration and randomisation – consider allowing testing in advance
- Make only minimal changes to CRF –knock on effect on database
- Easy identification of patients recruited under different versions of protocol (e.g. trial number)
- Consider any changes required to monitoring plan

Thank you

Any questions?

Acknowledgements:

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Leeds Institute of Molecular Medicine

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NCRN National Cancer Research Network