Understanding the role of QA in clinical trials

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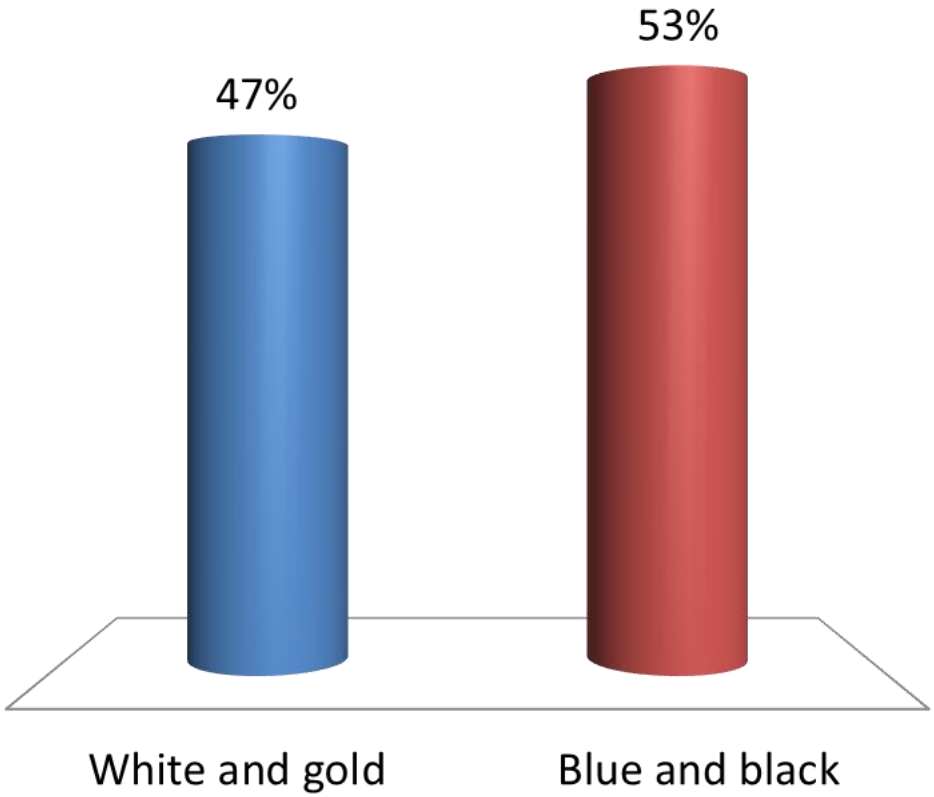
Introduction

QA for PBT trials

- Why do we do radiotherapy trials QA?
- Evaluating risks in radiotherapy clinical trials
- What QA should we be doing for proton trials?

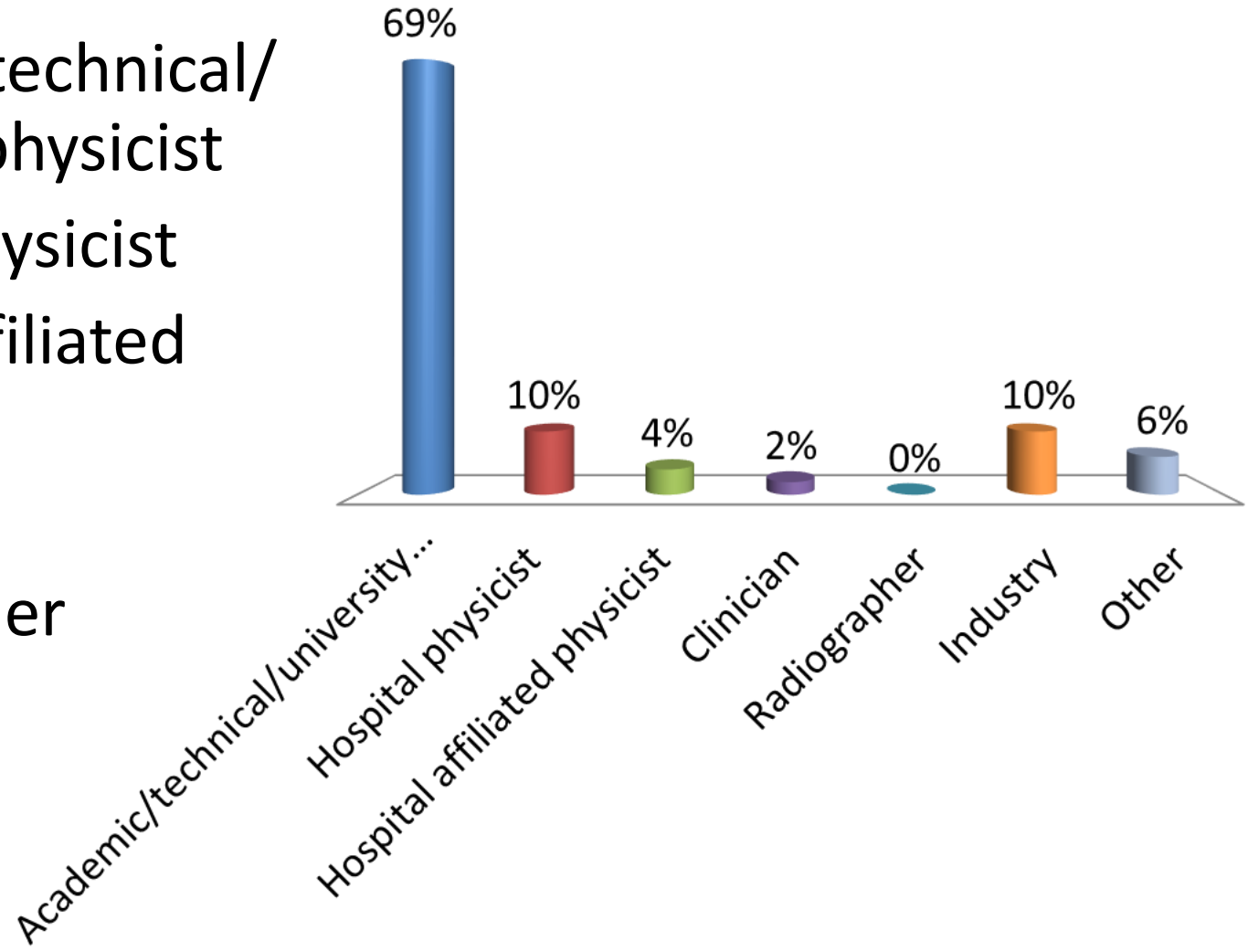
What colour is this dress

A. White and gold
B. Blue and black



Who is in the audience?

A. Academic/technical/ university physicist
B. Hospital physicist
C. Hospital affiliated physicist
D. Clinician
E. Radiographer
F. Industry
G. Other



Why do QA in trials?

Purpose of QA is to reduce risks

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Implementing a QA Programme

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"Quality comes not from inspection, but from improvement of the production process"

W. Edwards. Deming

Building in quality from the start

Trial protocols

- Clear and detailed protocol stating what is wanted

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Make use of existing standards

- Clinician Outlining
- Established standards of treatment (consensus)
- Dosimetry – Codes of Practice

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Training

- Workshops
- Planning and outlining benchmark cases, dosimetry audit – evaluation, feedback

Trial QA during recruitment

On-trial assessment

- "Prospective" : prior to treatment start
- "Retrospective": post treatment start

- Review of (for photons):
  - patient outlining
  - planning
  - IGRT

Trial protocols and QA

QA – ensuring centres comply with the protocol

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Results of QART assessment with patient outcome in prospective clinical trials.

Study [ref]	Type of QA	Number of cases evaluated *n* (%)	Minor deviations *n* (%)	Major deviations *n* (%)	Technical issues with QA review *n* (%)	Impact on clinical outcome	*p* Value
HD 4 [5]	R	368 (98.0)	–	141 (37.5)*	8 (2.1)	7-year RFS with D: 72% *vs.* 7-year RFS with no D: 84%	0.004
EORTC 20884 [2]	R	135 (88.8)	–	63 (46.7)	46 (30.3)	5-year RFS with D: 90% *vs.* 5-year RFS without D: 84%	0.31
RTOG 0411 [4]	R	NS	–	13 (13.4)	NS	Grade GI ⩾ 3 toxicity with D:45%‡ *vs.* Grade GI ⩾ 3 toxicity without D:18%‡	0.05
RTOG 9704 [1]	R	416 (92.2)	–	200 (48.0)**	14/35 (40.0)†	mOS with D: 1.46 yo *vs.* mOS without D: 1.74 yo	0.008
RTOG 0022 [8]	R	67 (97.0)	47 (89.0)	6(11.0)	14/67 (21.0)	LRF with major D: 50% *vs.* LRF with no major D: 6%	0.04
TROG 0202 [15]	P & R††	687 (80.5)‡‡	–	97 (11.8)	33/820 (4.0)	OS with major D: 70% *vs.* OS without major D: 50%	<0.001

Weber et al, QA makes a clinical trial stronger: Evidence-based medicine in radiation therapy. 2012, Radiother Oncol, 105, 4-8

Trial protocols and QA

Protocol deviations (D):

"with D"

"with no D"

Impact on clinical outcome	*p* Value
7-year RFS with D: 72% *vs.* 7-year RFS with no D: 84%	0.004
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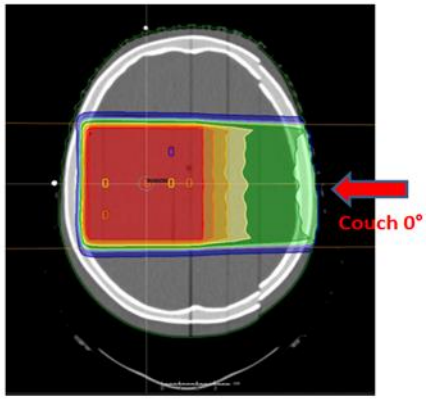
mOS with D: 1.46 yo *vs.* mOS without D: 1.74 yo	0.008
LRF with major D: 50% *vs.* LRF with no major D: 6%	0.04
OS with major D: 70% *vs.* OS without major D: 50%	<0.001

Abbreviations:
LRF, local-regional failures
mOS, median overall survival
RFS, relapse-free survival
GI, gastro-intestinal

Trial protocols: proton specifics

Standards:

- **On the way!**
- EPTN work groups
  - Planning and robustness
  - Dosimetry audit
  - HU-SPR audit
- Updated Codes of Practice
  - TRS- 398
  - IPEM CoP - NPL's portable graphite calorimeter



Recap of trial risks

- Trial cannot answer its research questions
- Trial will report misleading/unrepresentative results
- Trial results will not be repeatable
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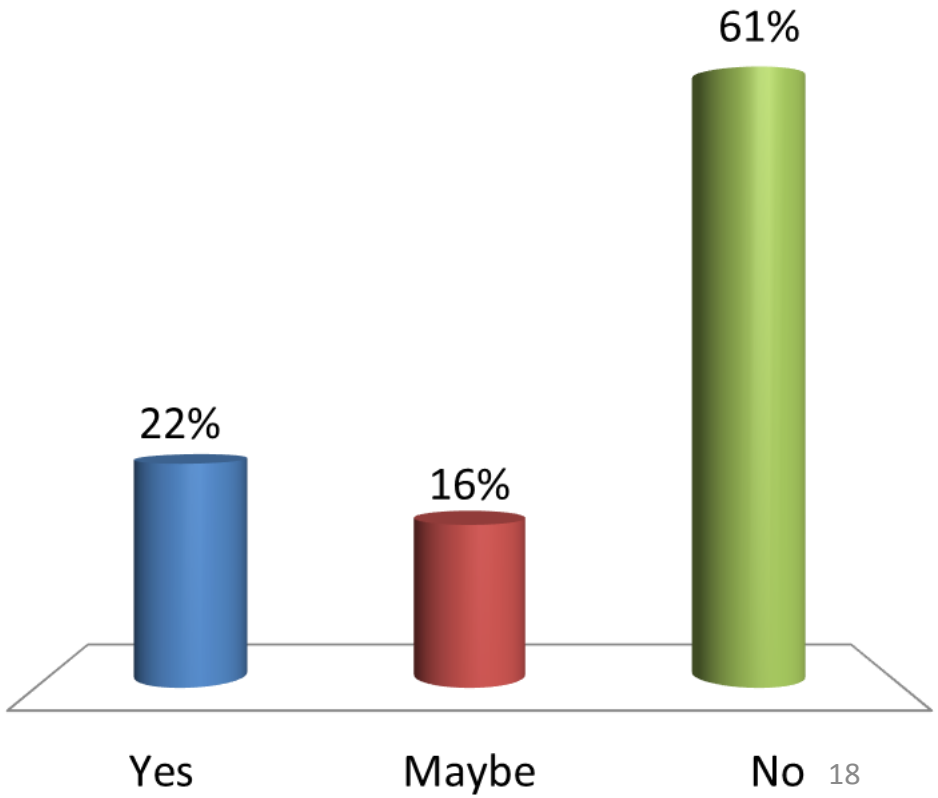
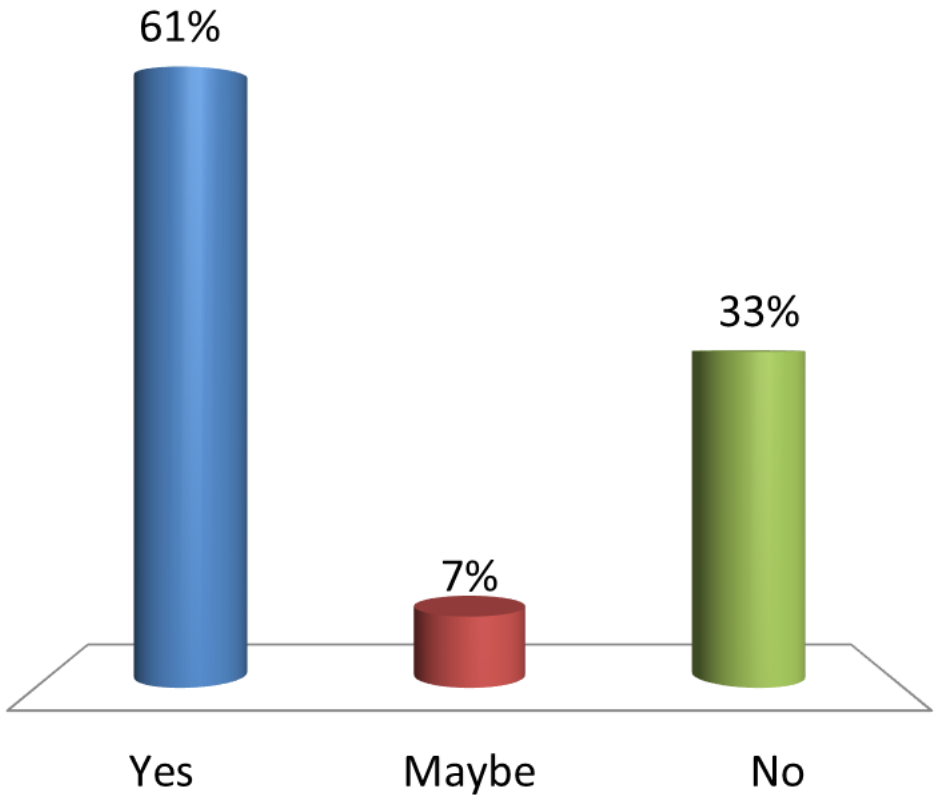
Protocol (based on photon experience) says that centres must use a GTV, CTV *and PTV*. The prescription dose must be normalised to mean PTV dose. A proton centre wishes to join the trial, but wants to use a robustly covered CTV, rather than PTV. **Should the centre be allowed to join the trial, using the centre's preferred technique?**

A. Yes
B. Maybe
C. No



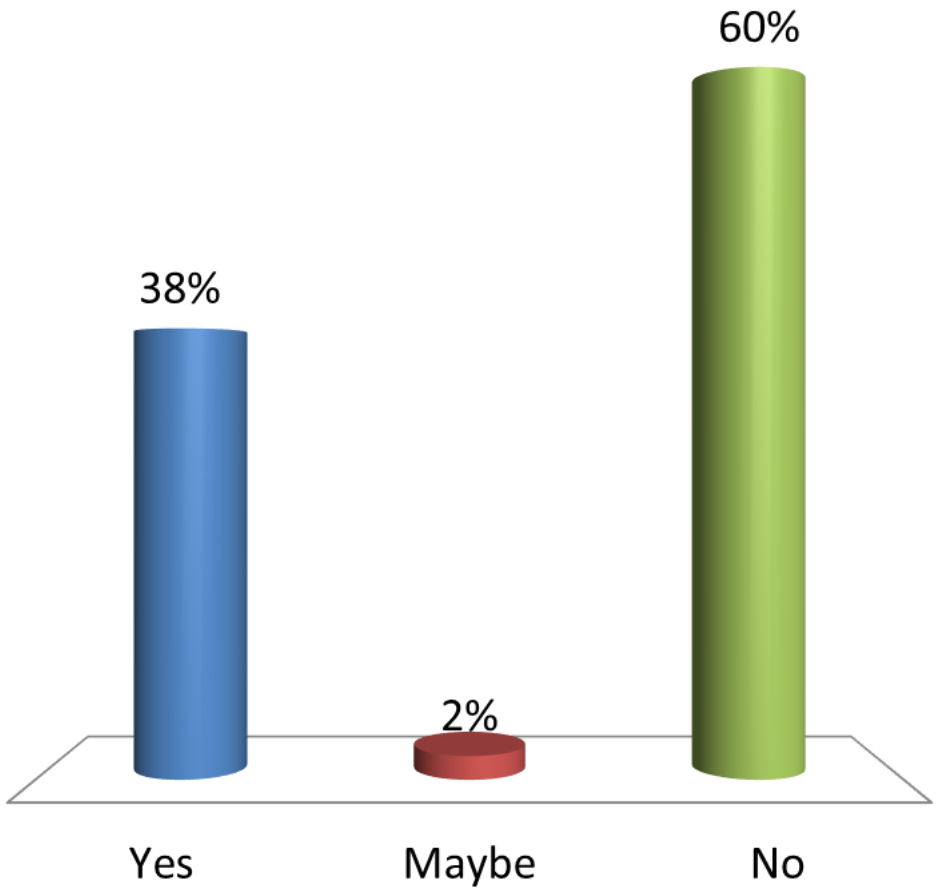
You are proposing an international H&N IMRT vs Proton trial. The trial will recruit for 3 years and report 3 years after that. Would you restrict the proton arm to centres with **pencil beam scanning**?

A. Yes
B. Maybe
C. No



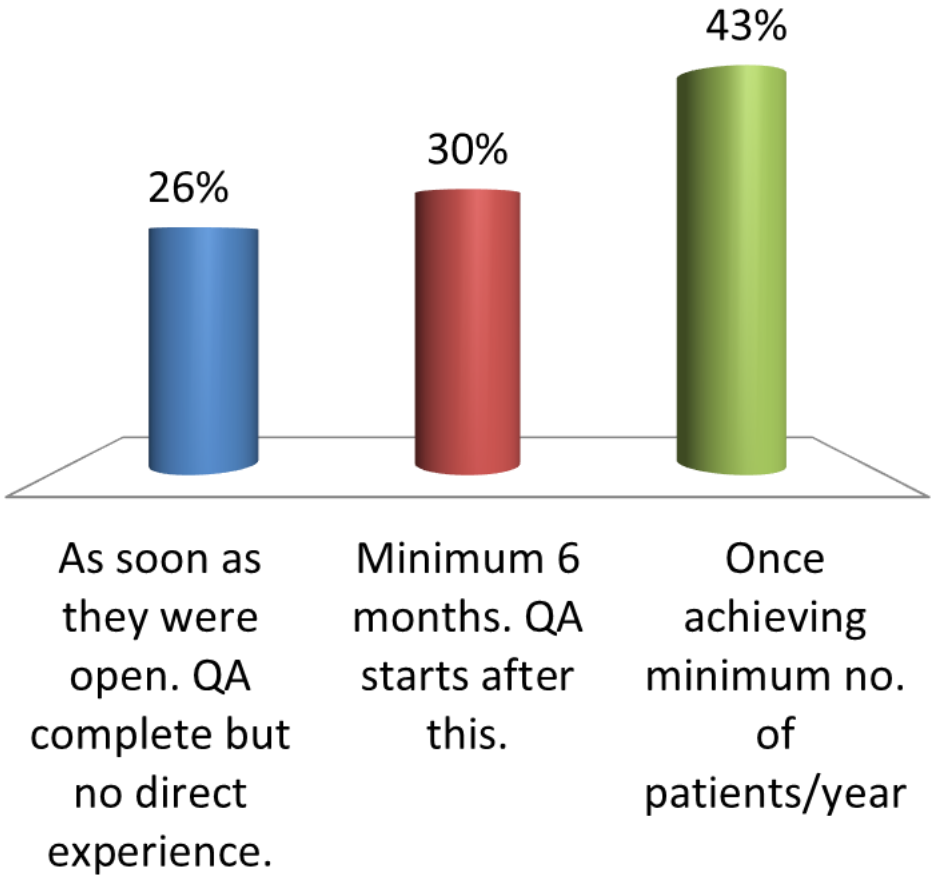
You are proposing an international H&N IMRT vs Proton trial. The trial will recruit for 3 years and report 3 years after that. Would you restrict the proton arm to centres with **gantry delivery**?

A. Yes
B. Maybe
C. No



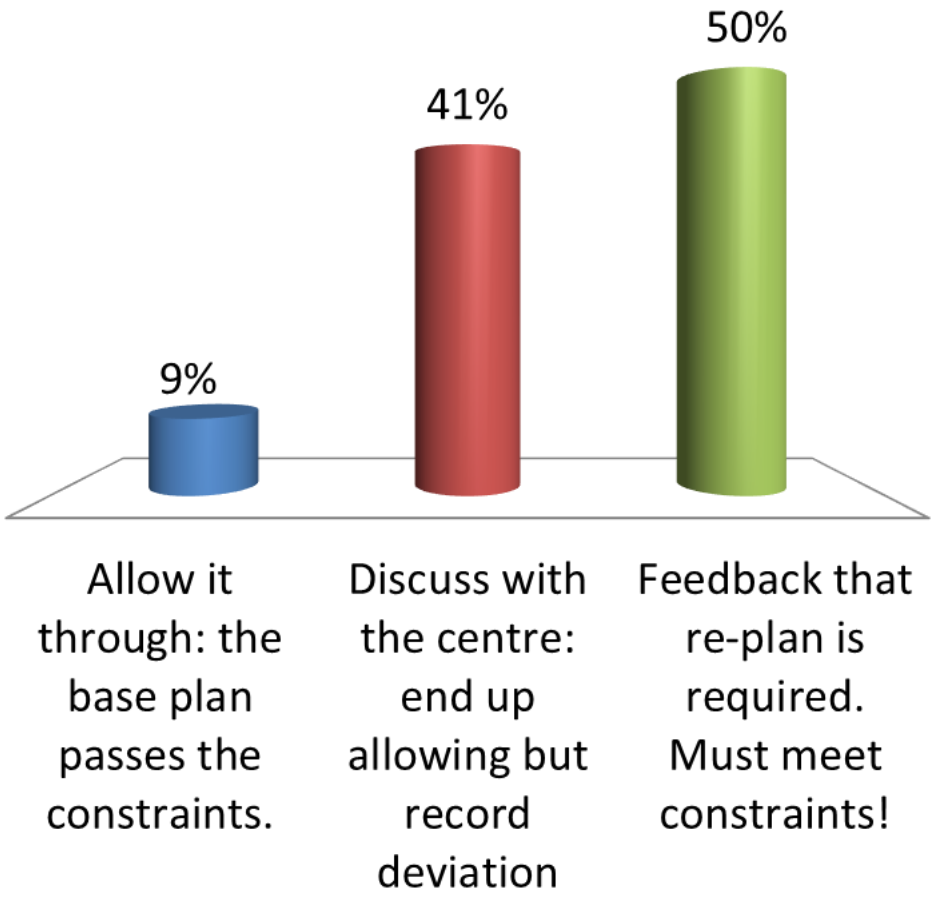
A **new** proton centre is looking to join a clinical trial. From a trial QA perspective, **at what point would you allow them to join?**

A. As soon as they were open. QA complete but no direct experience.
B. Minimum 6 months. QA starts after this.
C. Once achieving minimum no. of patients/year



A proton centre submits a plan for trial QA, including robustness analysis DVHs. The spinal cord mandatory dose constraint is exceeded when just the +3.5% error is applied and ~half of the +3.5% and 3mm shifts. Do you...

A. Allow it through: the base plan passes the constraints.
B. Discuss with the centre: end up allowing but record deviation
C. Feedback that re-plan is required. Must meet constraints!



Conclusion

- Trial QA is important:
  - Reduces variation, reduces risk and adds to trial strength
  - It is not perfect: involves opinion as well as facts
  - It will adapt with techniques and technology

Thank you

Questions?