PCTU
Pragmatic Clinical Trials Unit

Queen Mary
University of London
Barts and The London

Hospital based Trials within Cohorts

Professor HM (Lenny) Verkooijen

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Trials using cohorts: guidance on design, analysis and reporting with real-world examples

- Introduction to Trials within Cohorts
- Hospital based Trials within Cohorts
- Analysis of Trials within Cohorts
- Ethics of Trials within Cohorts

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Trials using cohorts: guidance on design, analysis and reporting with real-world examples

- Introduction to Trials within Cohorts
- Hospital based Trials within Cohorts
- Analysis of Trials within Cohorts
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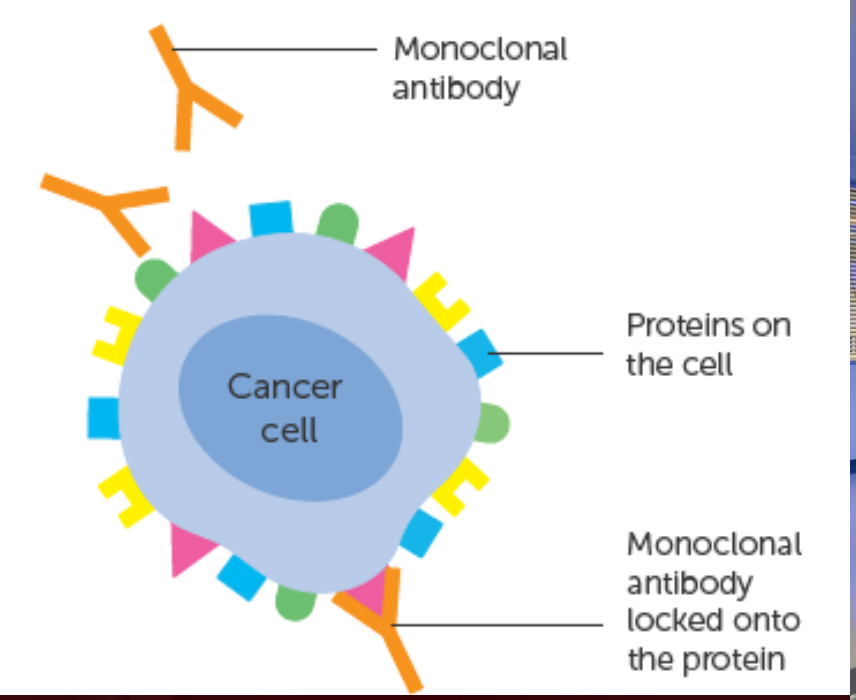
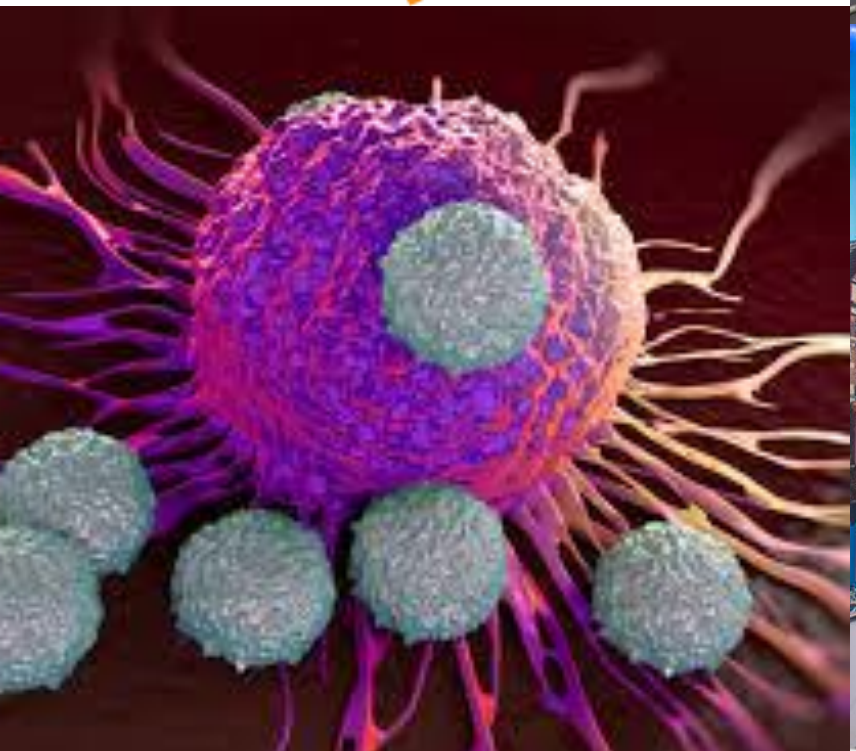
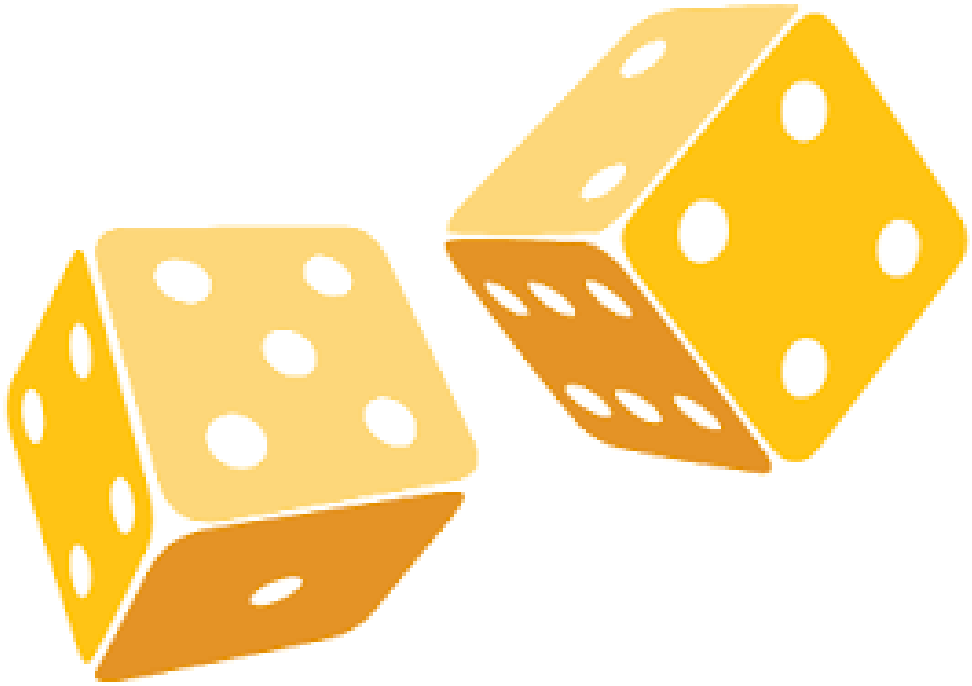

Monoclonal antibody
Cancer cell
Proteins on the cell
Monoclonal antibody locked onto the protein


MAQUET




Elekta
UNITY 2



Classic RCTs are challenging

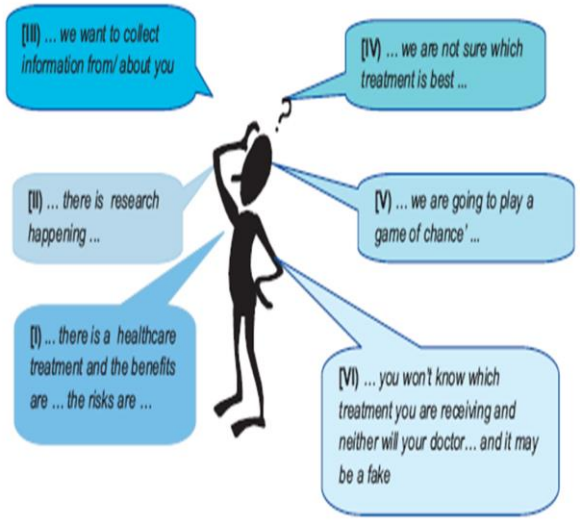
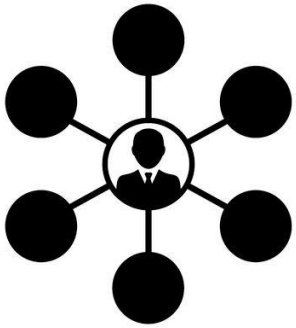
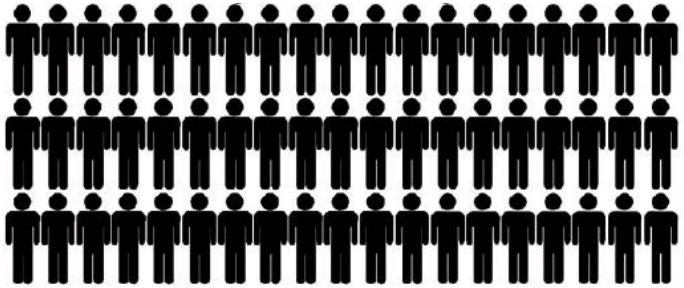


Figure 1 Informed consent – key messages from the patient's perspective.

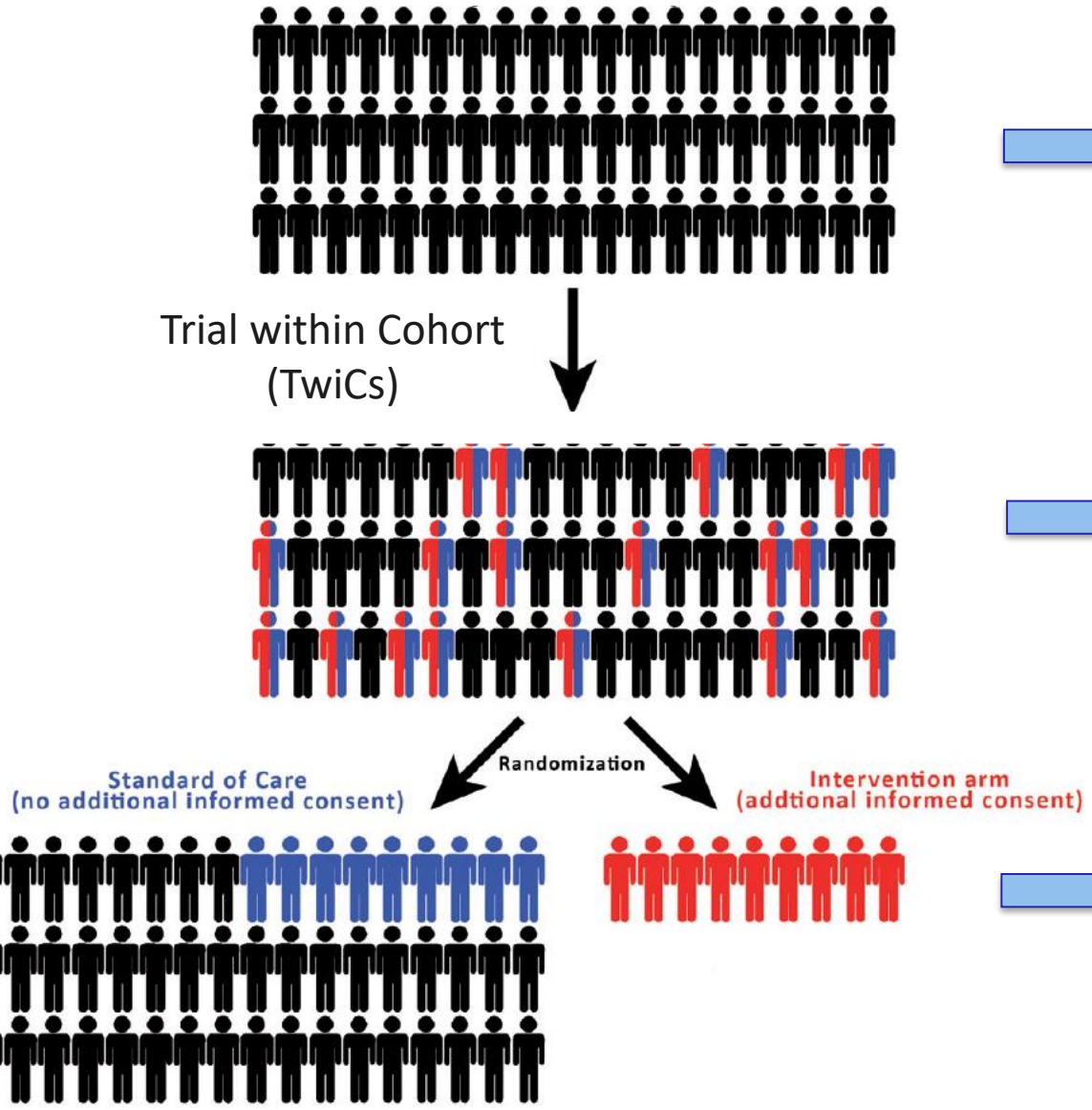
Classic RCTs in Intervention Oncology face additional challenges





Cohort
Registry
Routine Care
……..

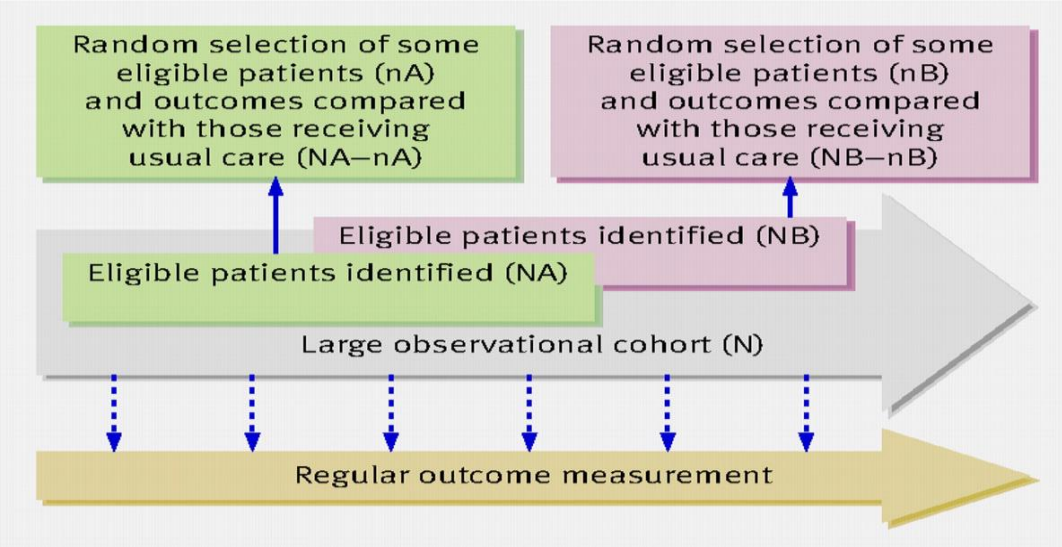
Regular outcome measurement



Regurlar outcome measurement

Challenges of TwiCs in the hospital setting

1. Ethics - Staged Informed Consent
2. Infrastructure to 'Learn from every patient'
3. Sequential vs. batch recruitment in dynamic cohort



Relton 2010 BMJ

IRB UMC Utrecht / CCMO*

"Inform patients clearly of what it means to be allocated to a TwiCs control arm."

- Serving as control without knowing it
- Being (temporarily) ineligible for other TwiCs / intervention studies (without knowing it)

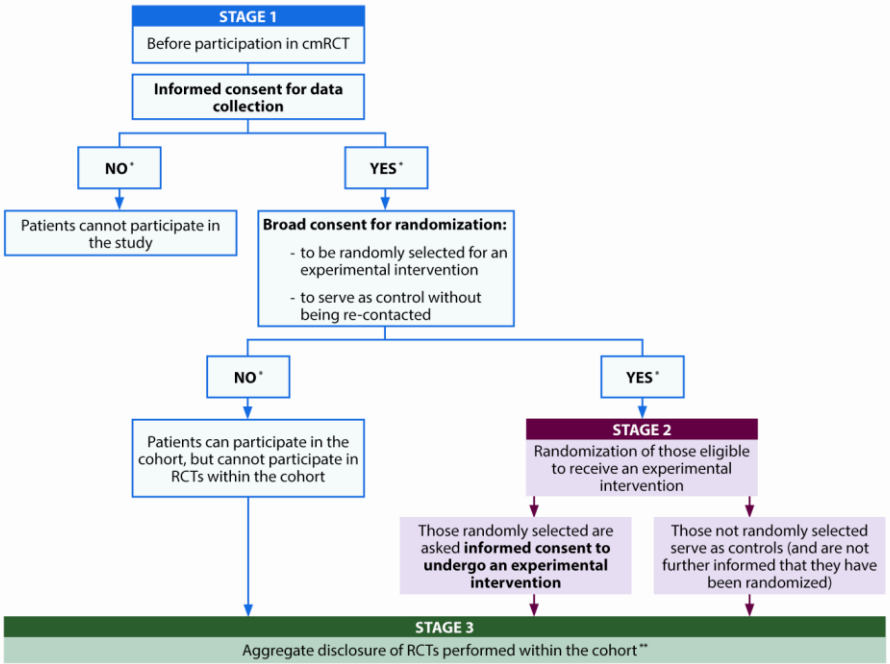
** Central Committee on Research involving Human Subjects*

Staged-informed Consent in the Cohort Multiple Randomized Controlled Trial Design

Danny A. Young-Afat,[a,b] Helena A. M. Verkooijen,[c] Carla H. van Gils,[a] Joanne M. van der Velden,[b] Johannes P. Burbach,[b] Sjoerd G. Elias,[a] Jonannes J. van Delden,[d] Clare Relton,[e] Marco van Vulpen,[b] and Rieke van der Graaf[d]

Epidemiology • Volume 27, Number 3, May 2016

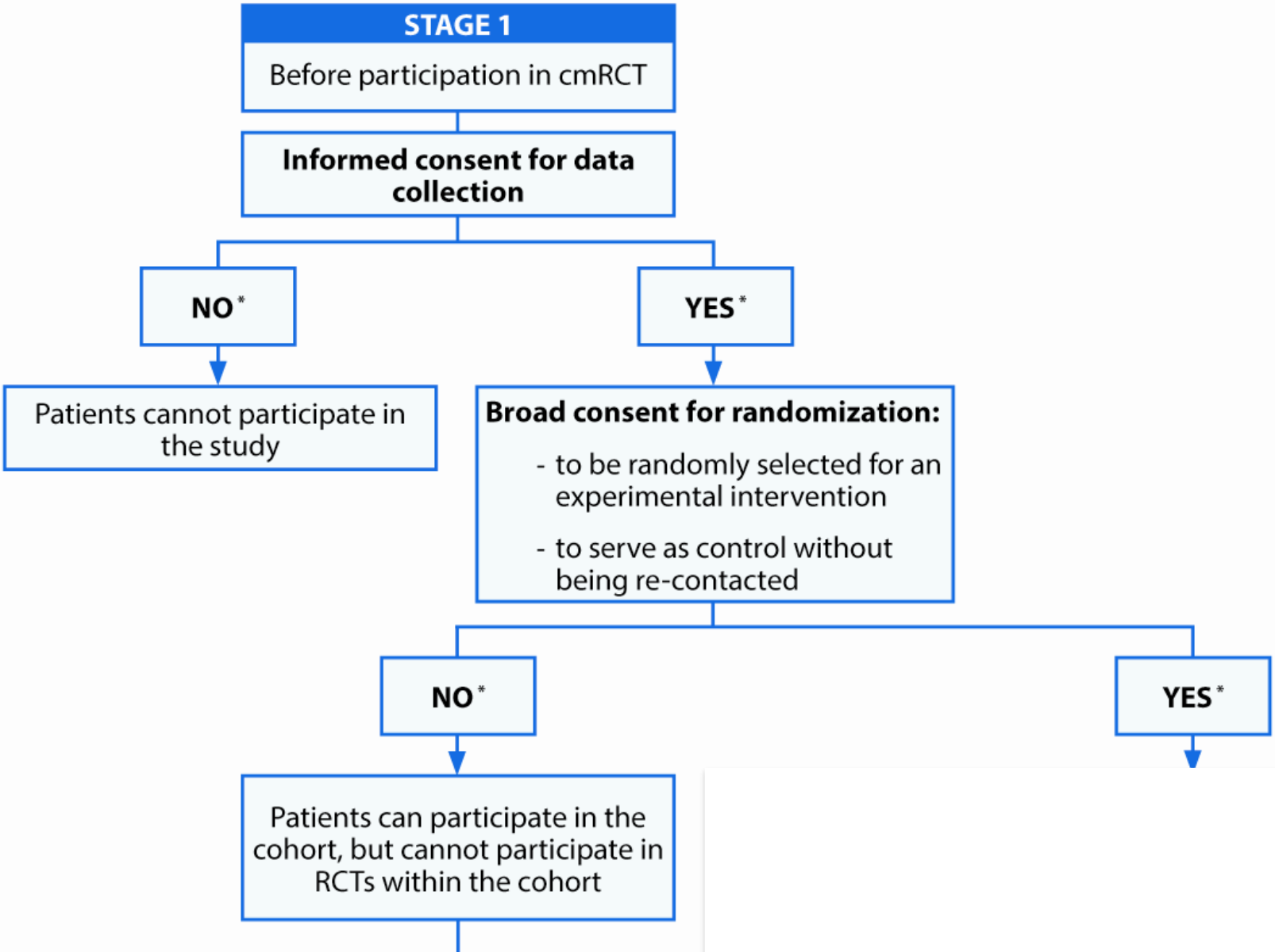
Staged-informed consent model for cmRCT

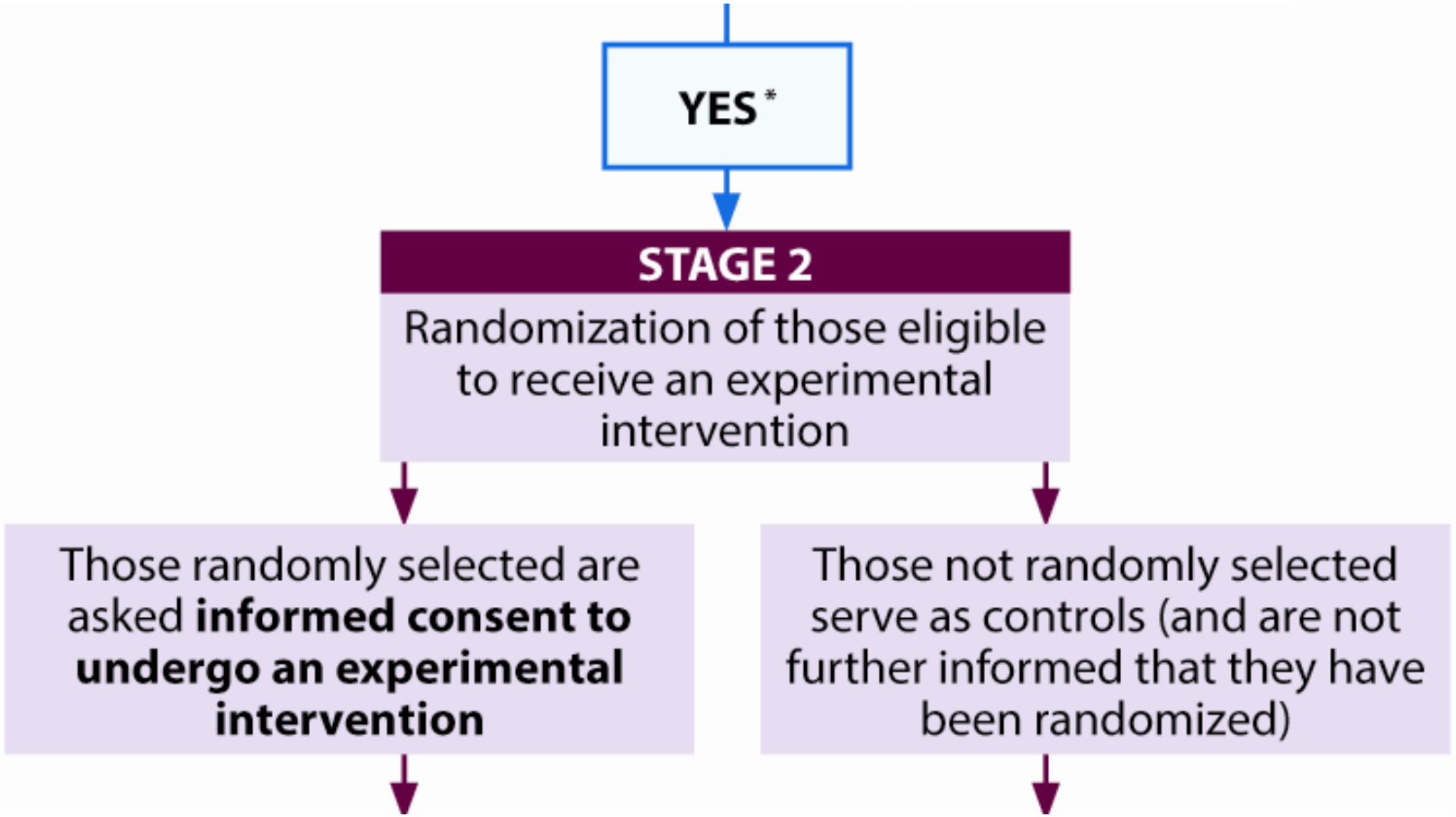


*Dynamic informed consent model which enables participants to change their previous 'yes or no' preference at any moment in time

**Only provided to those who opted-in for aggregrate disclosure (asked in stage 1).

Staged-informed consent model for cmRCT




YES *
STAGE 2
Randomization of those eligible to receive an experimental intervention
Those randomly selected are asked **informed consent to undergo an experimental intervention**
Those not randomly selected serve as controls (and are not further informed that they have been randomized)

*Dynamic informed consent model which enables participants to change their previous ' yes or no' preference at any moment in time

**Only provided to those who opted-in for aggregrate disclosure (asked in stage 1).

The Innovation Clinic

Informed consent

Re-use of clinical data

Biobanking

Patient reported outcomes

Extra scans

……..

profiles

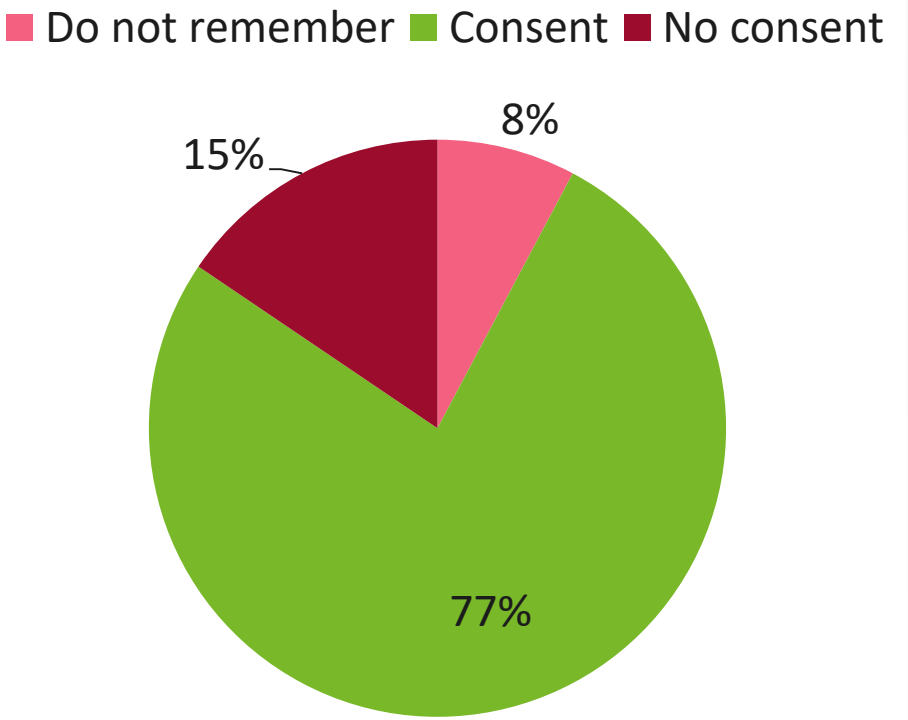
Broad consent for randomization

Our hospital TwiCs infrastructure

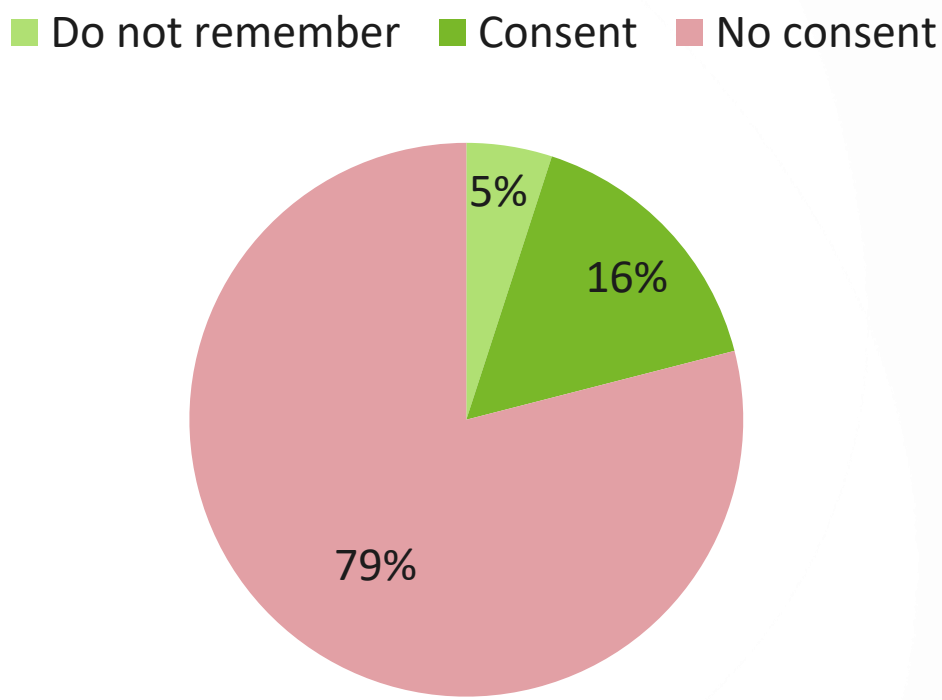
Cohort	**Site**	**n**	**Broad consent for randomization**
UMBRELLA (regional)	Breast	3500+	82%
PLCRC (national)	Colorectal	11000+	83%
PLCRC-Urect	*Rectal*	*1600+*	*85%*
PRESENT	Bone metastases	2000+	81%
OLYMPOS	Lymph nodes	200+	76%
COIMBRA	Brain metastases	170+	72%
UPC (regional)	Prostate	400+	79%
U-Color	Lung	100+	56%

‘Did you give broad consent for future randomization?’

Young-Afat et al. J Clin Epi 2020



Broad consent given
N=249



Broad consent refused
N=63

Clinical Investigation

Pain Response After S
Therapy Versus Conver
in Patients With Bone
Randomized Controlle
Prospective Cohort

Bart J. Pielkenrood, MD,* Joanr
Yvette M. van der Linden, MD, F
Nicolien Kasperts, MD,* Joost J
Wietse S. C. Eppinga, MD,* Roxa
Jorrit J

The impact of retractor SPONGE-assisted laparoscopic surgery on duration of hospital stay and postoperative complications in patients with colorectal cancer (SPONGE trial): study protocol for a randomized controlled trial

Alice M. Couwenberg[1*], Maarten J. P. Burbach[1], Anke B. Smits[2], Marco Van Vulpen[1], Wilhemina M. U. Van Grevenstein[3], Peter G. Noordzij[4] and Helena M. Verkooijen[5]

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Stereotactic Body Radiation
Conventional Radiation Therapy
Bone Metastases—A Phase 2
trolled Trial Within a
rt

,* Joanne M. van der Velden, MD, PhD,†
D,*
MD, PhD‖

Circulating tumor DNA guided adjuvant chemotherapy in stage II colon cancer (MEDOCC-CrEATE): study protocol for a trial within a cohort study

S. J. Schraa[1†], K. L. van Rooijen[1†], D. E. W. J. Simmons[4], V. M. H. Coupé[5], W. M. U. va D. van den Broek[9], G. A. Meijer[2], V. E. Velc behalf of the PLCRC-MEDOCC group

Assessing the effect of hyperbaric oxygen therapy in breast cancer patients with late radiation toxicity (HONEY trial): a trial protocol using a trial within a cohort design

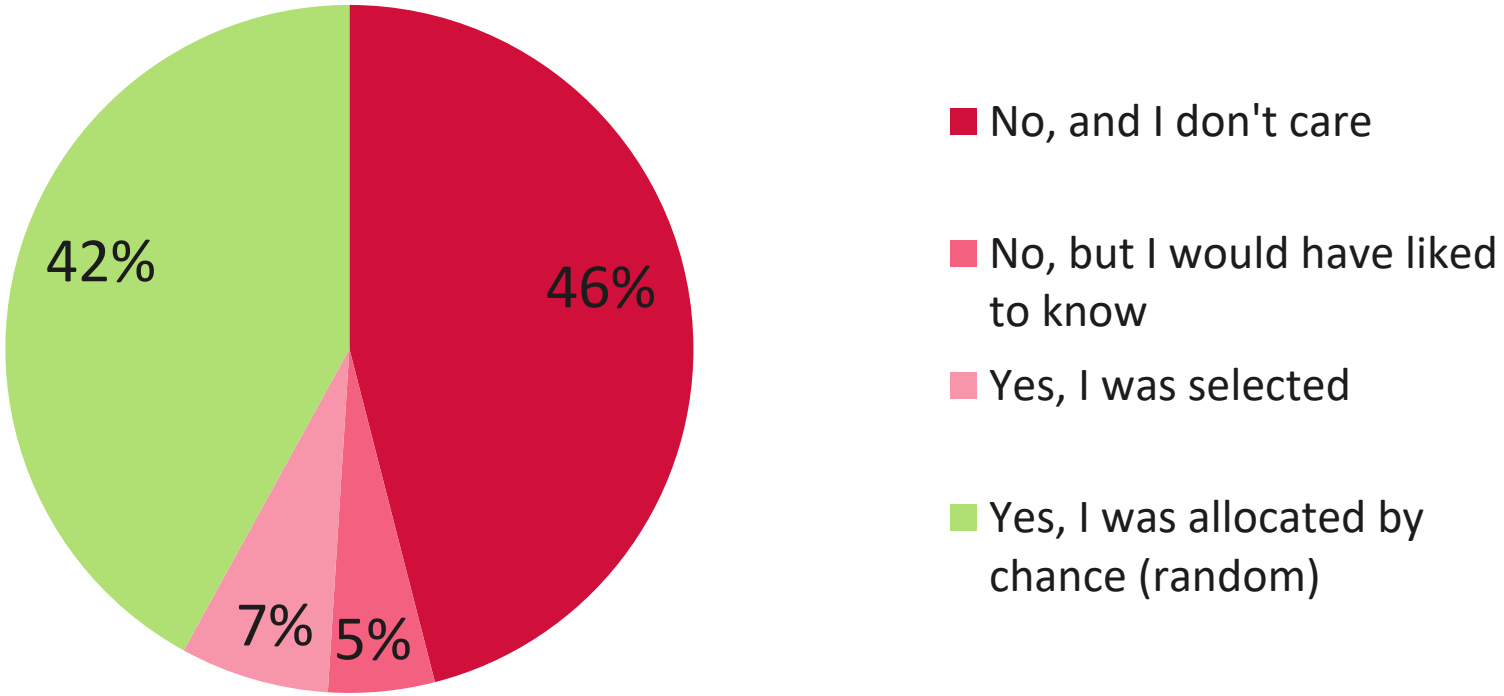
M. C. T. Batenburg[1*], H. J. G. D. van den Bongard[1], C. E. Kleynen[1], W. Maarse[2], A. Witkamp[3], M. Ernst[4], A. Doeksen[5], T. van Dalen[6], M. Sier[5,7], E. J. P. Schoenmaeckers[8], I. O. Baas[9] and H. M. Verkooijen[10]

The effects of exercis of patients with breas UMBRELLA Fit study): randomized controlle

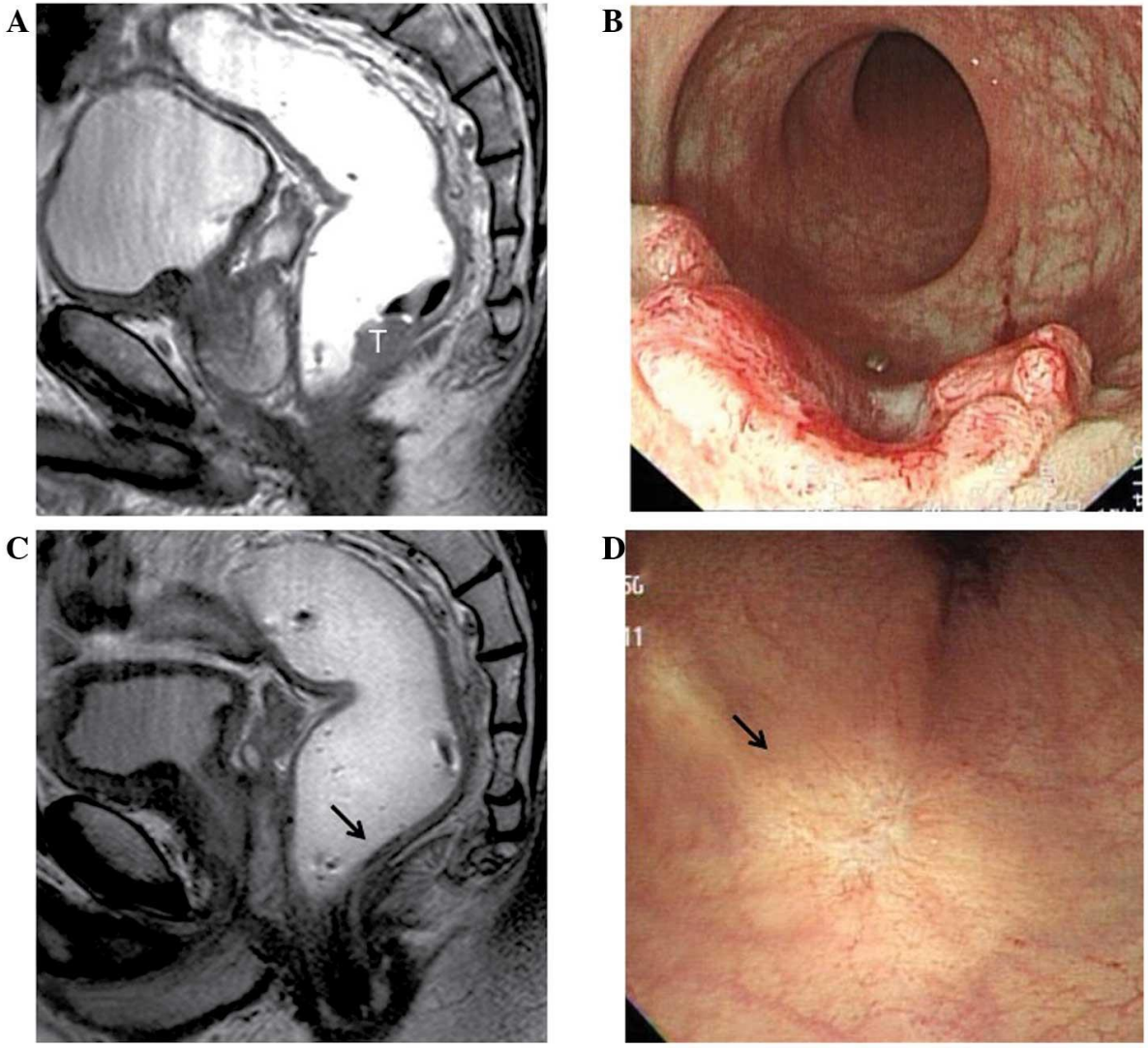
Roxanne Gal[1], Evelyn M. Monninkhof[1], Rolf H. H. Groenwold[1], Carla H. van Gils[1], Desiree H. J. G. van den Bongard[2], Petra H. M. Peeters[1], Helena M. Verkooijen[3] and Anne M. May[1*]

‘Do you understand how you have been selected for the experimental intervention?’

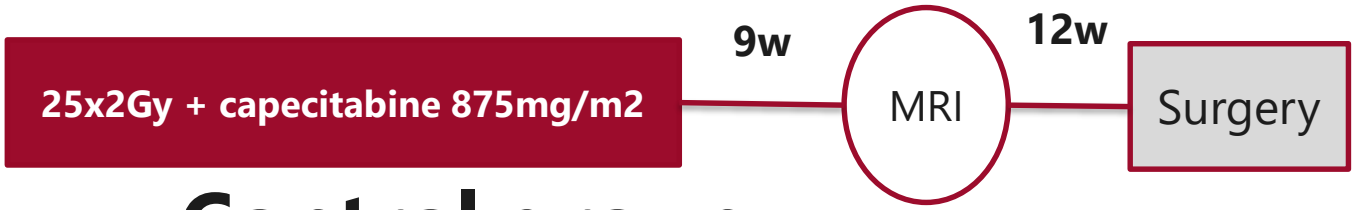
N=108



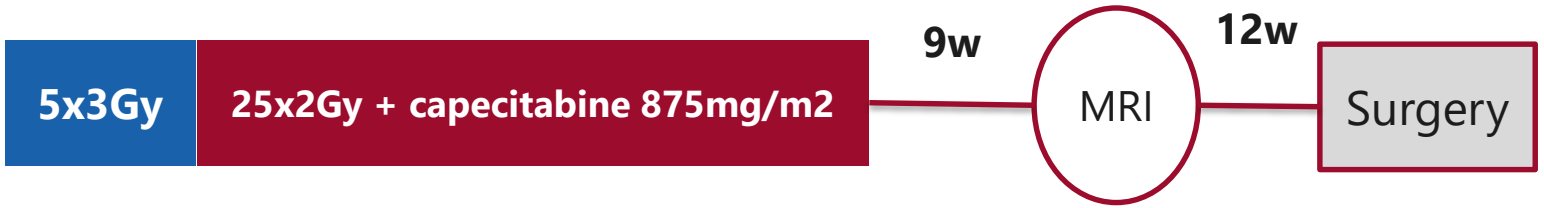
Young-Afat et al. J Clin Epi 2020


A
T
B
C
D

Does a 15 Gy radiation boost increase the probability of pathological complete response in patients with locally advanced rectal cancer?



Control group



Intervention group

Couwenberg et al. Int J Radiat Oncol Biol Phys 2020.

Random selection of eligible patients offered a BOOST

Patients eligible for the RECTAL BOOST

Prospective Data Collection Initiative on Colorectal Cancer (PLCRC)

PROSPECTIEF LANDELIJK CRC COHORT

Regular outcome measurements

Relton 2010 BMJ

UMC Utrecht

Timing of Randomisation

ELSEVIER

Check for updates

Journal of Clinical Epidemiology

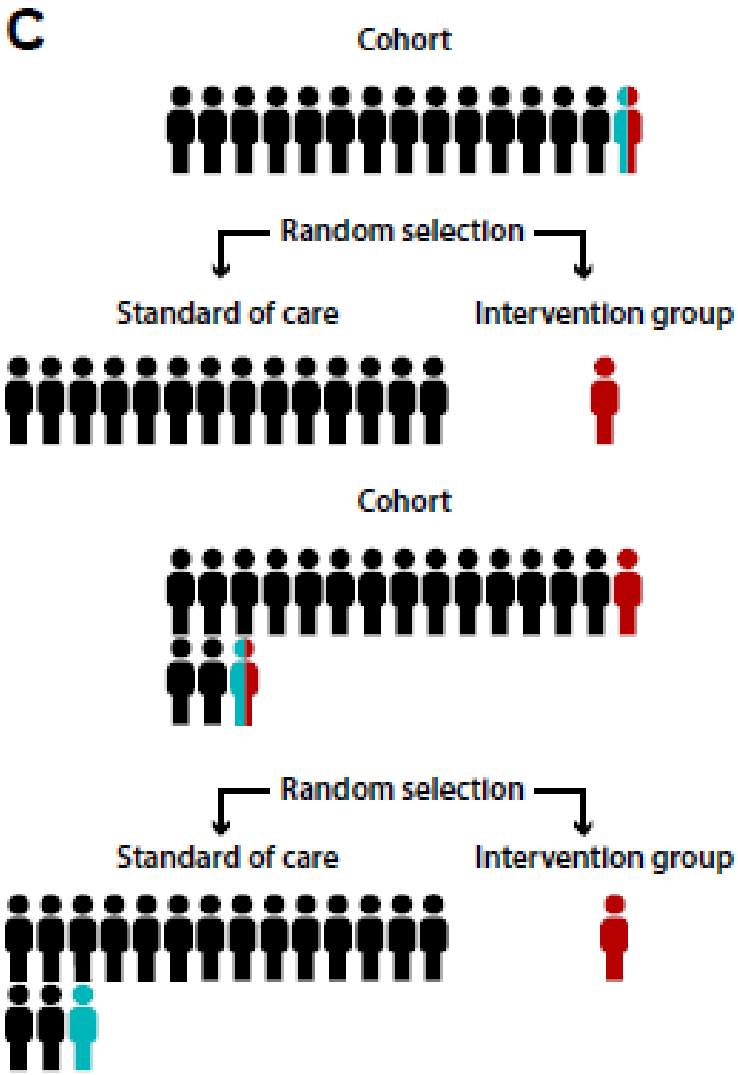
Journal of Clinical Epidemiology 120 (2020) 33–39

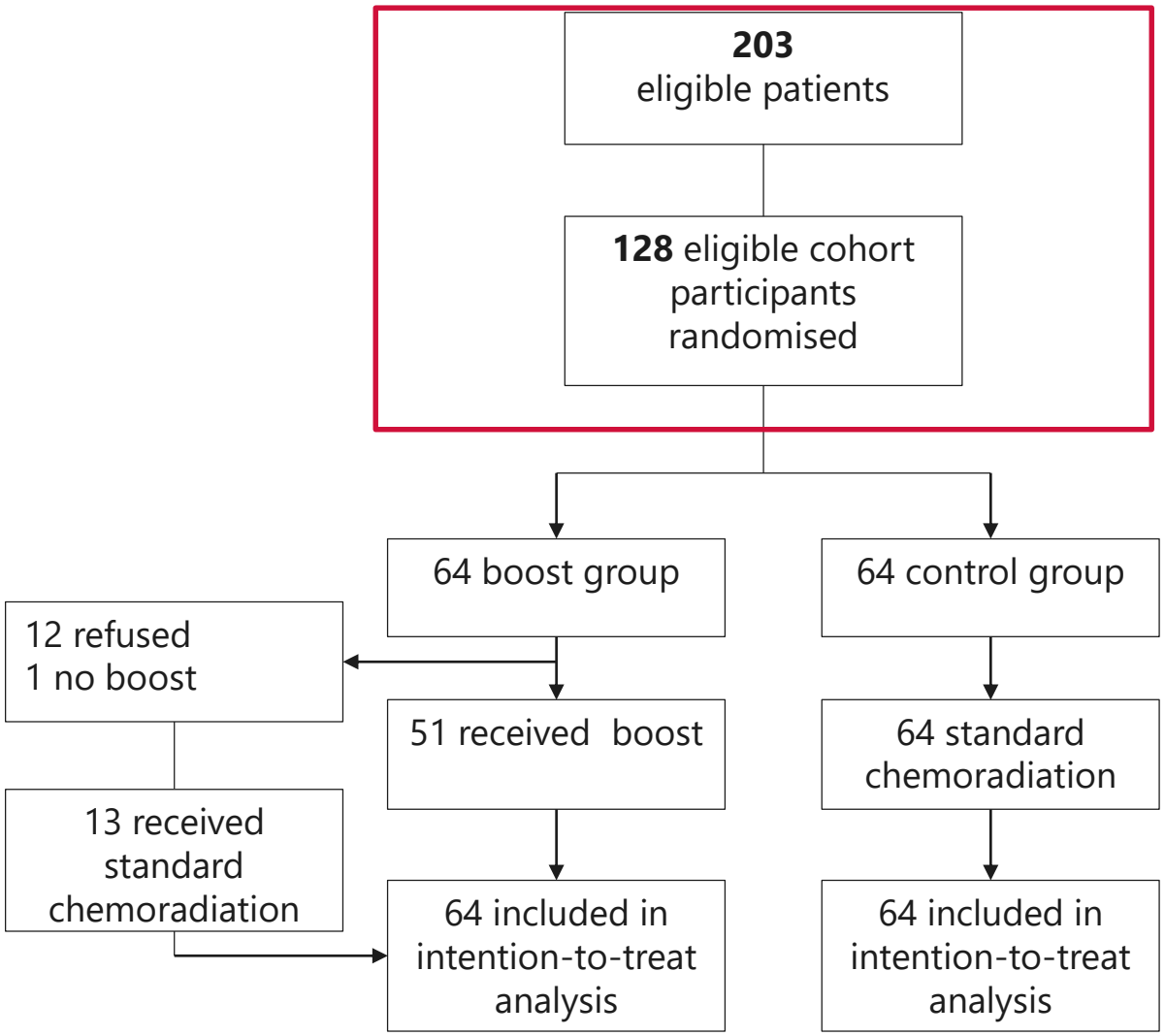
ORIGINAL ARTICLE

The trials within cohorts design facilitated efficient patient enrollment and generalizability in oncology setting

Alice M. Couwenberg[a,*], Johannes P.M. Burbach[b], Anne M. May[c], Maaike Berbee[d], Martijn P.W. Intven[a], Helena M. Verkooijen[e,f]

Sequential randomization in dynamic cohort

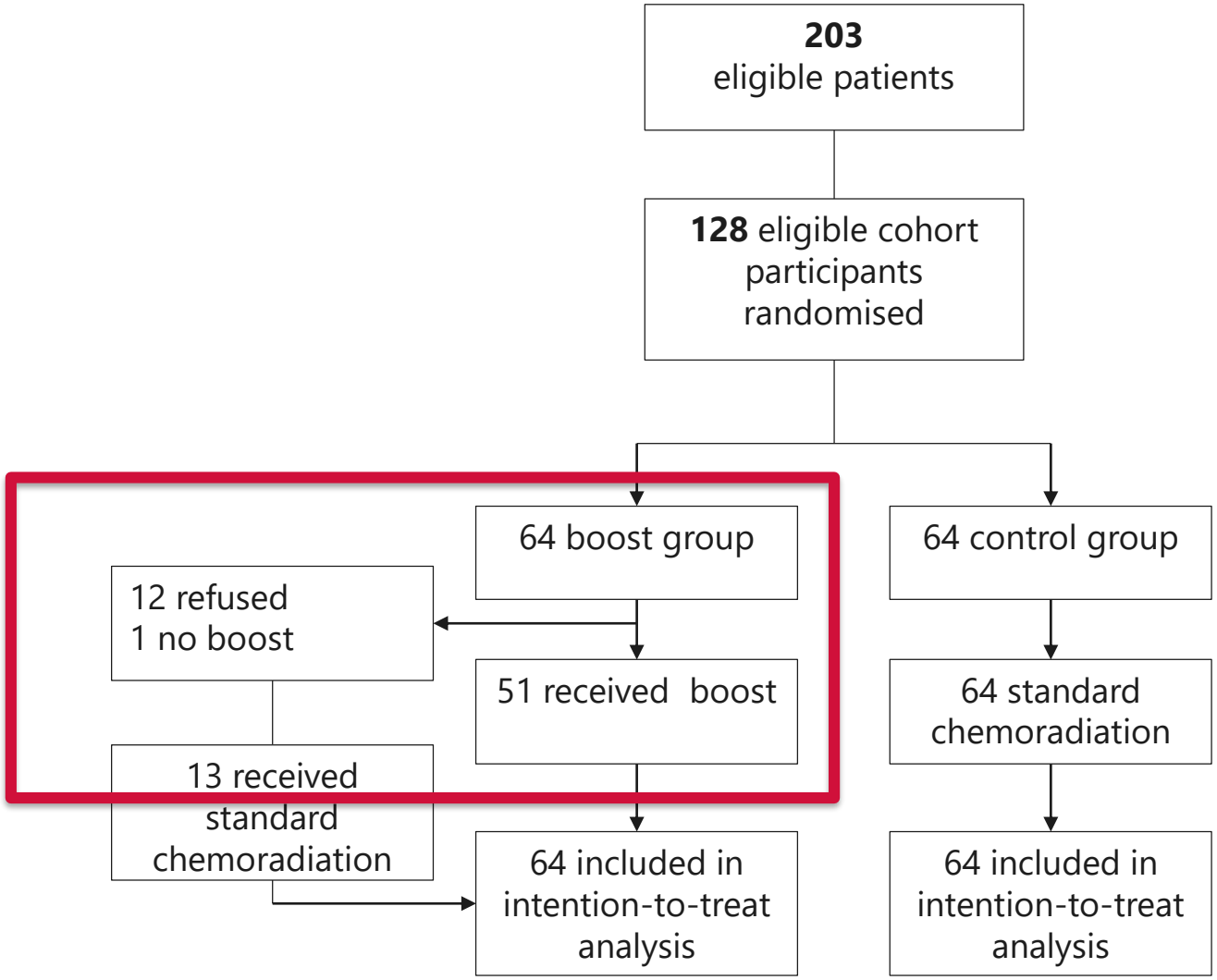




63%

Couwenberg et al. Int J Radiat Oncol Biol Phys 2020.

	RECTAL BOOST	General rectal cancer population (IKNL)
Age, median years (IQR)	64 (55 – 70)	65 (57 – 70)
Male	95 (74.2%)	240 (60.6%)
No comorbidity	57 (44.5%)	174 (43.9%)
T2	7 (5.5%)	28 (7.1%)
T3	90 (70.3%)	251 (63.4%)
T4	31 (24.2%)	117 (29.5%)
Clinically node negative	14 (10.9%)	37 (9.3%)


203
eligible patients
128 eligible cohort participants randomised
64 boost group
64 control group
12 refused
1 no boost
51 received boost
64 standard chemoradiation
13 received standard chemoradiation
64 included in intention-to-treat analysis
64 included in intention-to-treat analysis

63%

81%

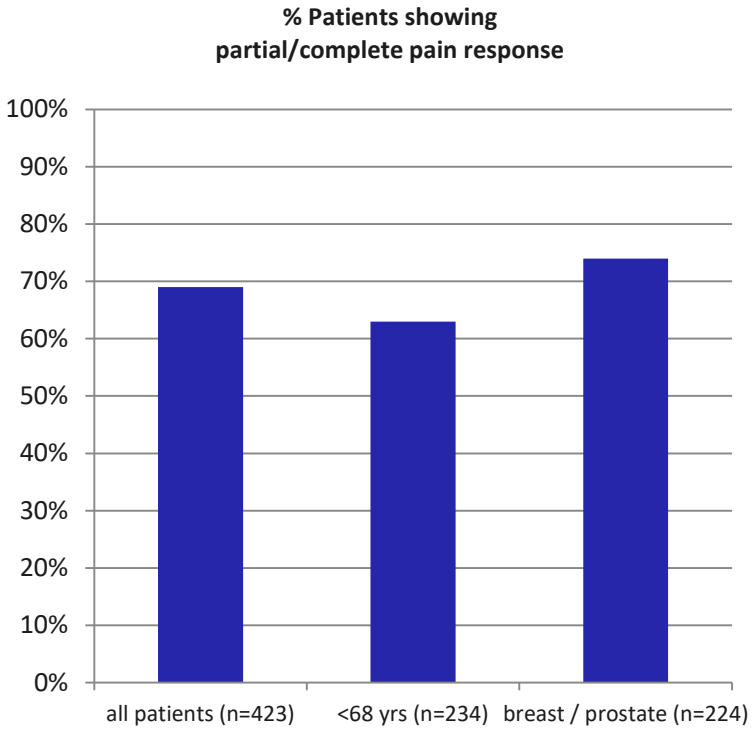
Results

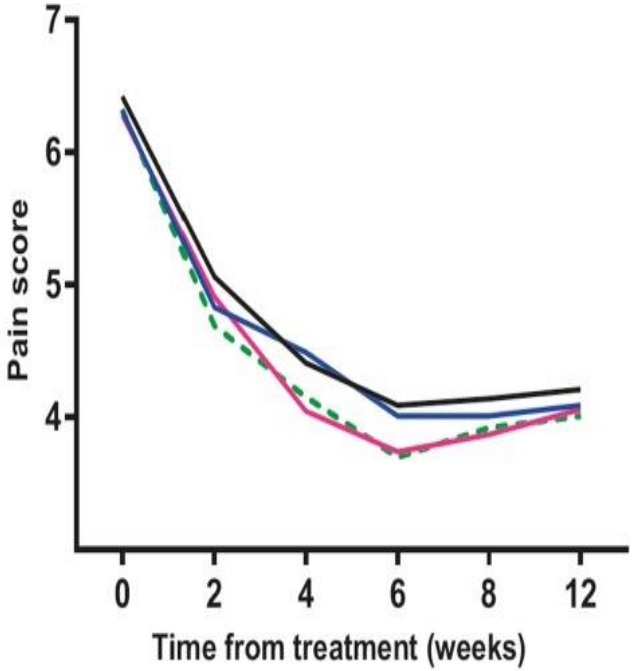
Primary outcome

BOOST (n=64)	CONTROL (n=64)	P-value
36%	37%	0.86

Couwenberg et al. Int J Radiat Oncol Biol Phys 2020.

PRESENT cohort – metastatic bone disease





All patients	416	224	186	208	207	190
Patients with spinal metastases	278	175	125	135	137	122
Patients with breast or prostate cancer	215	123	111	129	127	119
Patients in good physical condition	200	120	98	112	114	106

Journal of Radiation Oncology (2018) 7:325–333

STUDY PROTOCOL Open Access

Stereotactic versus conventional radiotherapy for pain reduction and quality of life in spinal metastases: study protocol for a randomized controlled trial

Pètra Braam[1*], Philippe Lambin[2] and Johan Bussink[1]

BMC Cancer

STUDY PROTOCOL Open Access

Comparing conVEntional RadioTherapy with stereotactIC body radiotherapy in patients with spinAL metastases: study protocol for an randomized controlled trial following the cohort multiple randomized controlled trial design

Joanne M. van der Velden[1*], Helena M. Verkooijen[1,2], Enrica Seravalli[1], Jochem Hes[1], A. Sophie Gerlich[1], Nicolien Kasperts[1], Wietse S. C. Eppinga[1], Jorrit-Jan Verlaan[3] and Marco van Vulpen[1]

STUDY PROTOCOL Open Access

Stereotactic versu nal radiotherapy for on and quality of life in spinal m udy protocol for a randomized rial

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BMC Cancer

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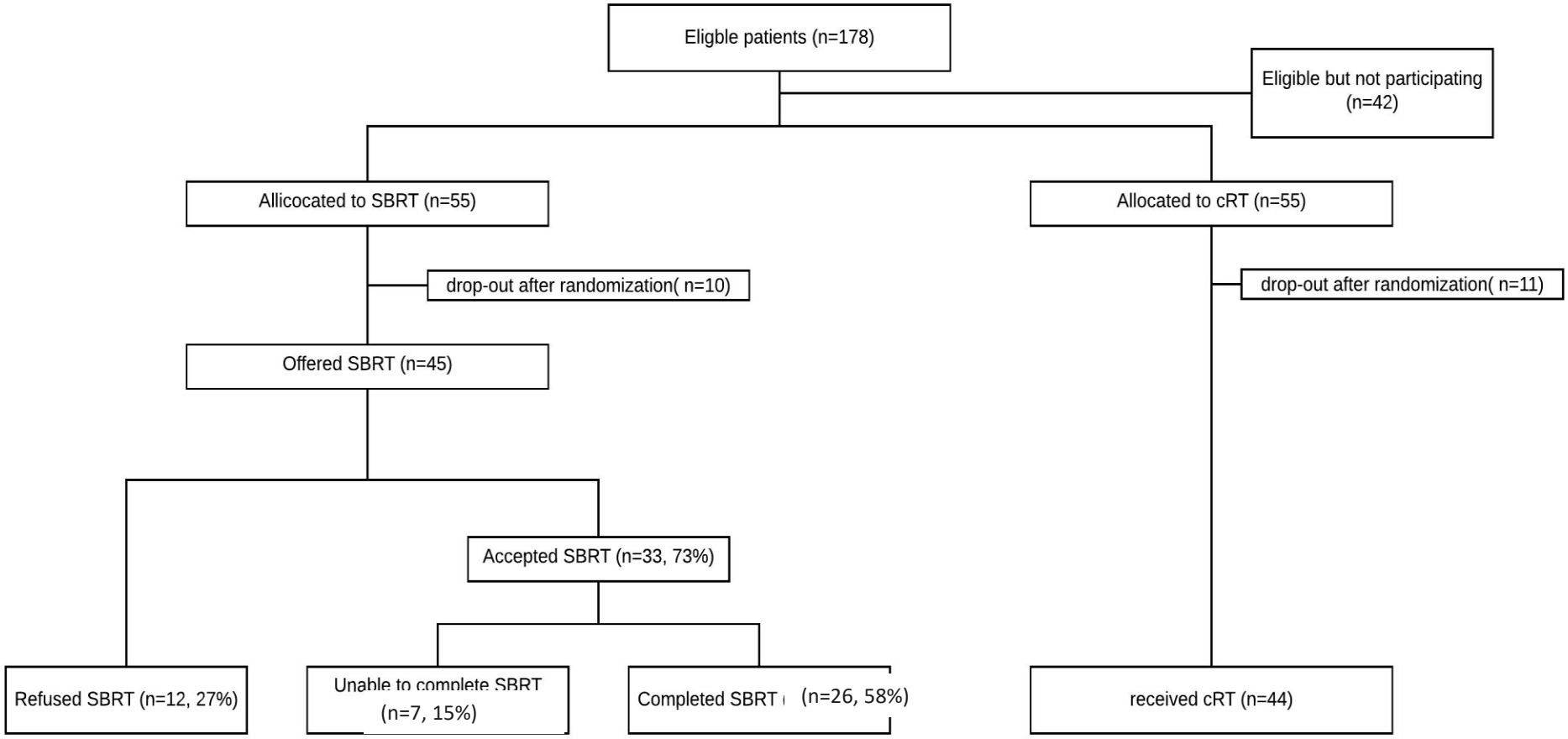
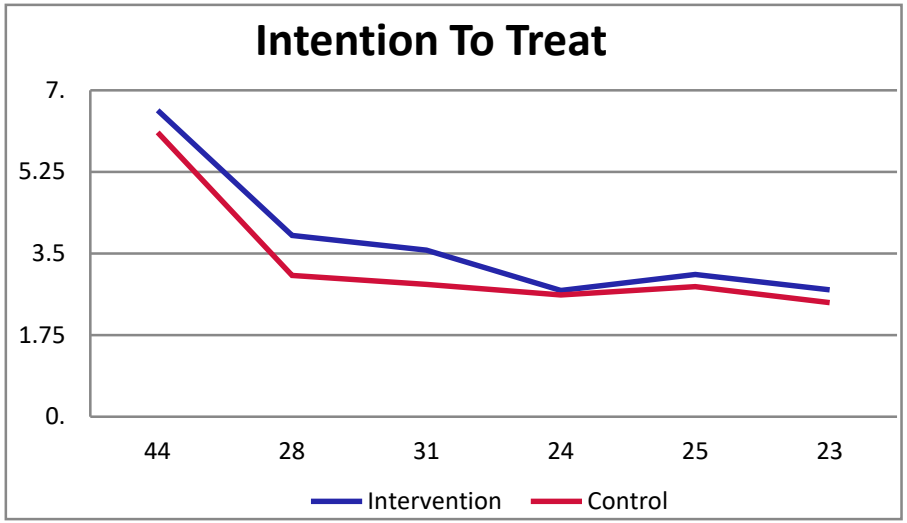
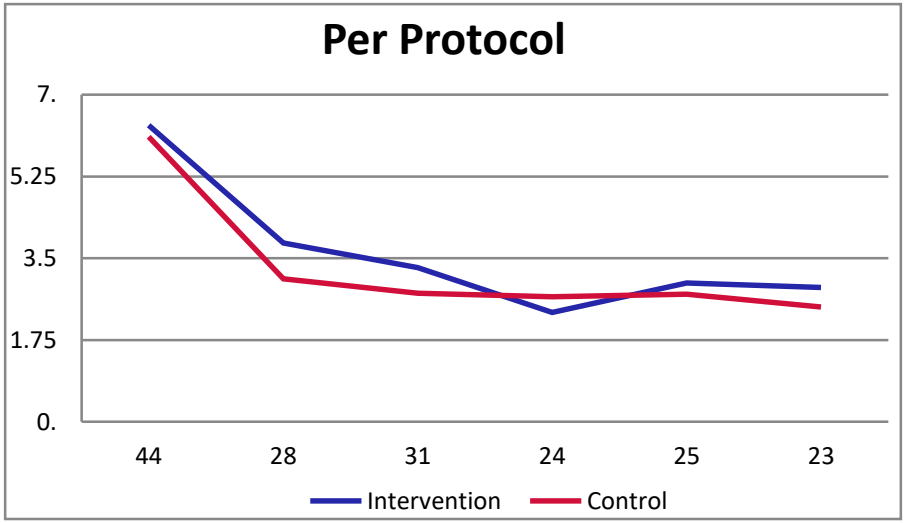
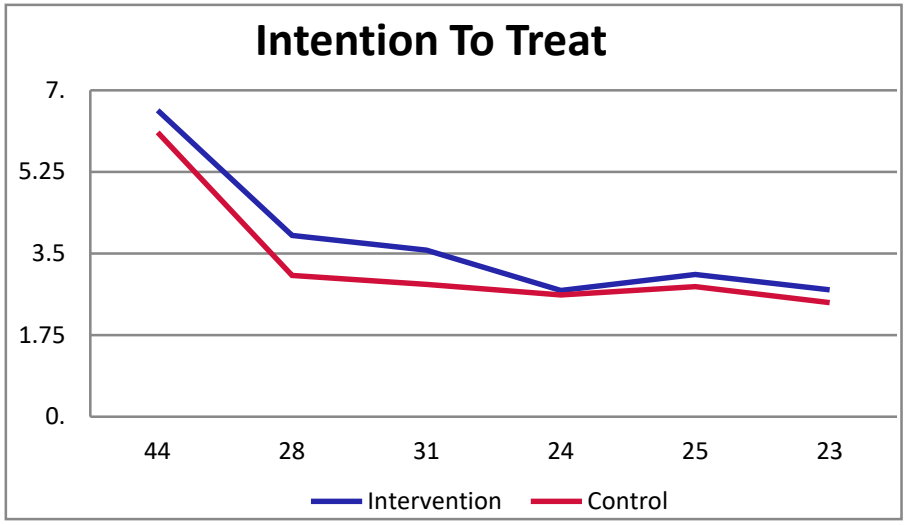
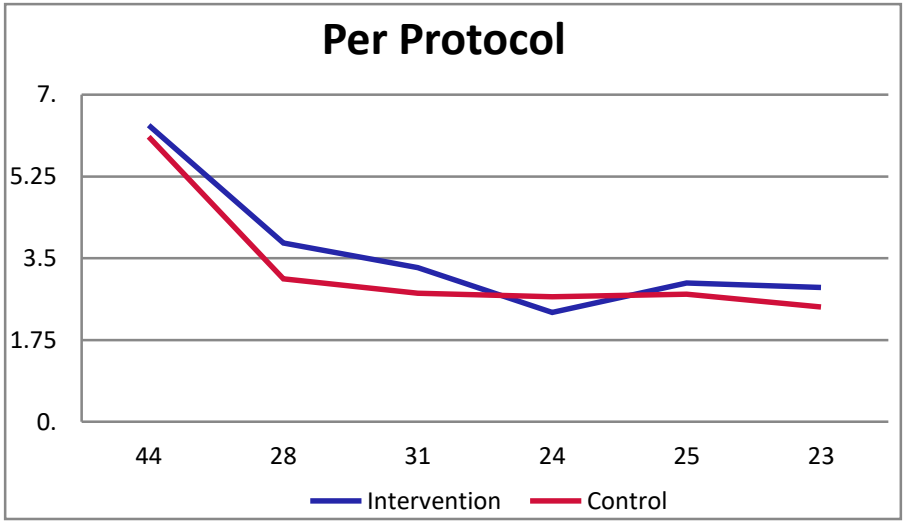

Eligble patients (n=178)
Eligible but not participating (n=42)
Allicocated to SBRT (n=55)
Allocated to cRT (n=55)
drop-out after randomization(n=10)
drop-out after randomization(n=11)
Offered SBRT (n=45)
Accepted SBRT (n=33, 73%)
Refused SBRT (n=12, 27%)
Unable to complete SBRT (n=7, 15%)
Completed SBRT (n=26, 58%)
received cRT (n=44)





Mean pain scores





Original Report

RTOG 0631 phase 2/3 study of image guided stereotactic radiosurgery for localized (1-3) spine metastases: Phase 2 results

Samuel Ryu MD [a,*], Stephanie L. Pugh PhD [b], Peter C. Gerszten MD, MPH [c], Fang-Fang Yin PhD [d], Robert D. Timmerman MD [e], Ying J. Hitchcock MD [f], Benjamin Movsas MD [a], Andrew A. Kanner MD [g], Lawrence B. Berk MD [h], David S. Followill PhD [i], Lisa A. Kachnic MD [j]

International trial
65 institutions
N=339
Recruitment 2009 – 2018

'No difference in pain response between SBRT and conventional RT for patients with spinal metastases'

Astro, Chigago, 2019

Exercise group

Control group

UMBRELLA FIT

Prospective cohort

(UMBRELLA cohort)

UMBRELLA

Subpopulation

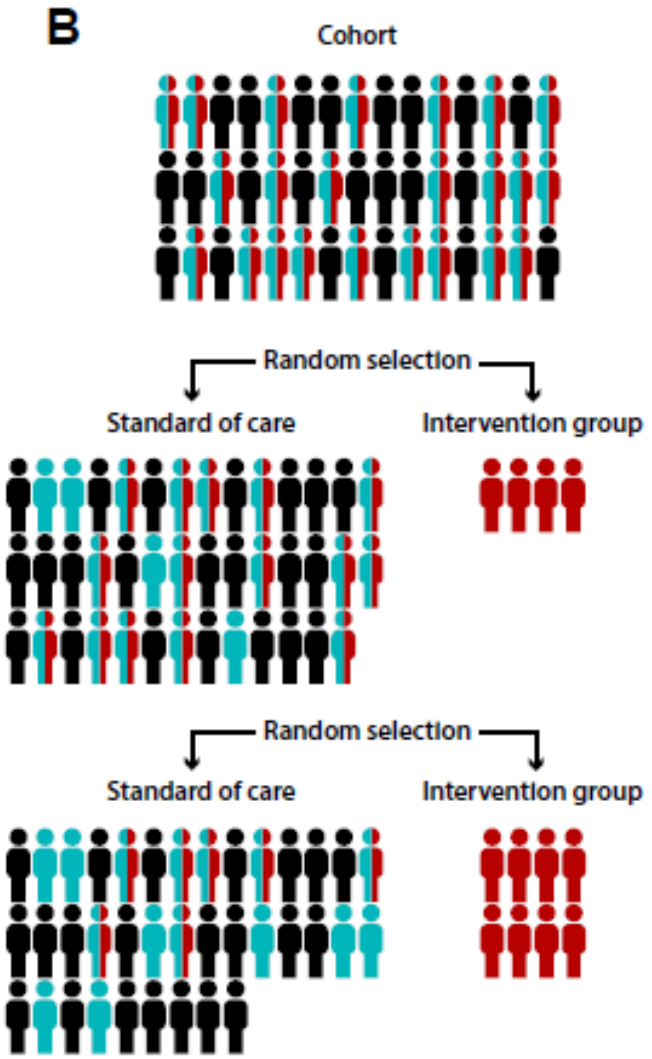
Repeated measurements →

Inclusio (intake Radiotherapy) 3-m 6-m 12-m 18-m 24-m 30-m 36-m etc. (up to 10 years)

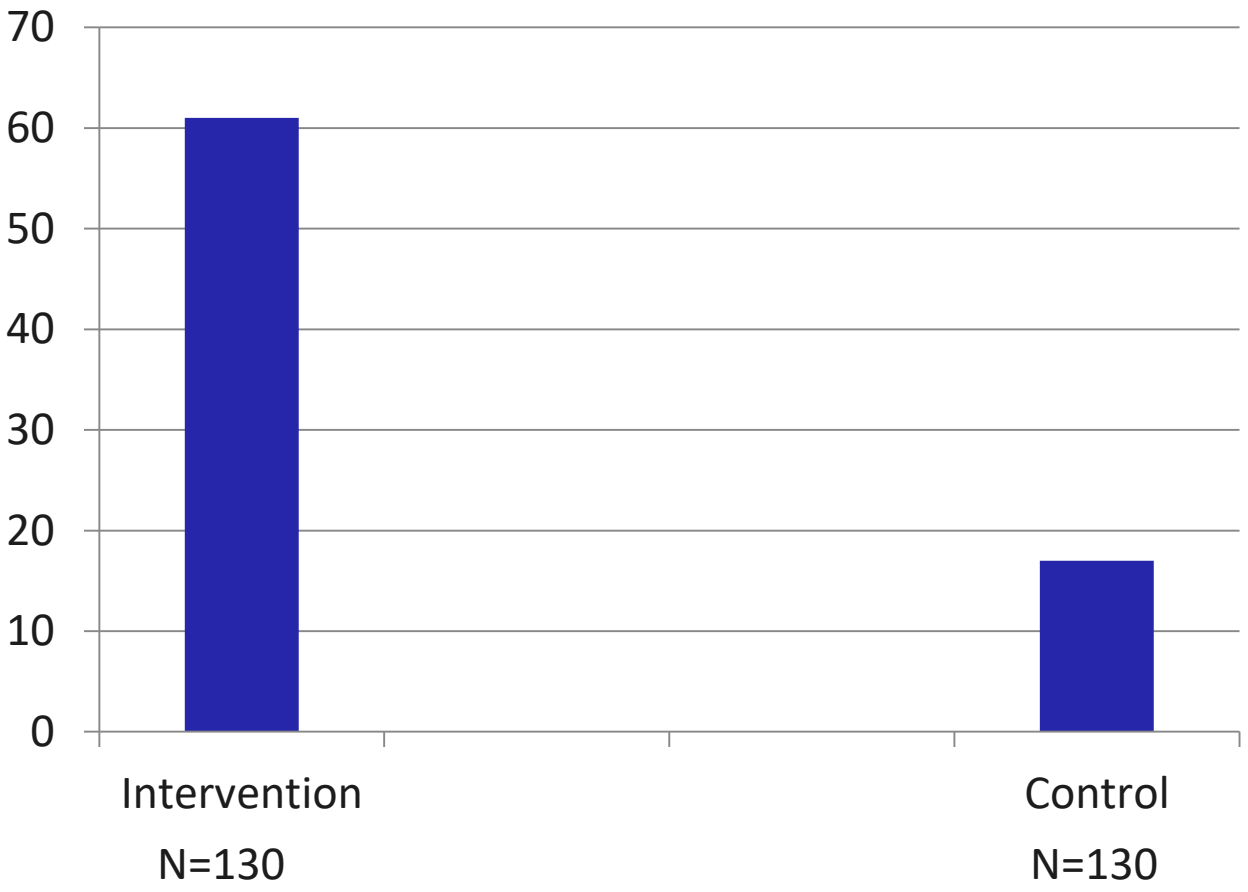
UMBRELLA Fit inclusion and follow-up

UMBRELLA FIT

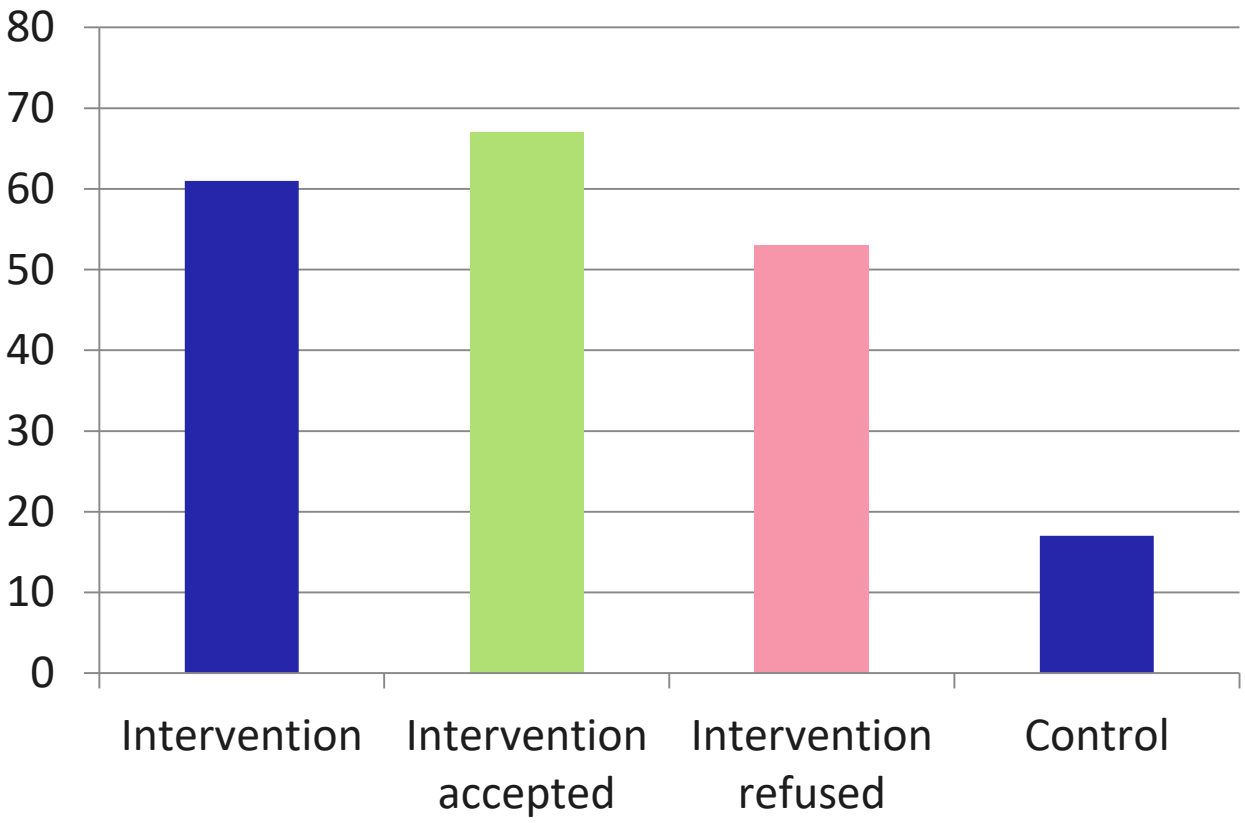
Batch randomization in (dynamic) cohort



Change in physical activity level
Between baseline to 6-months follow-up
(minutes per week)

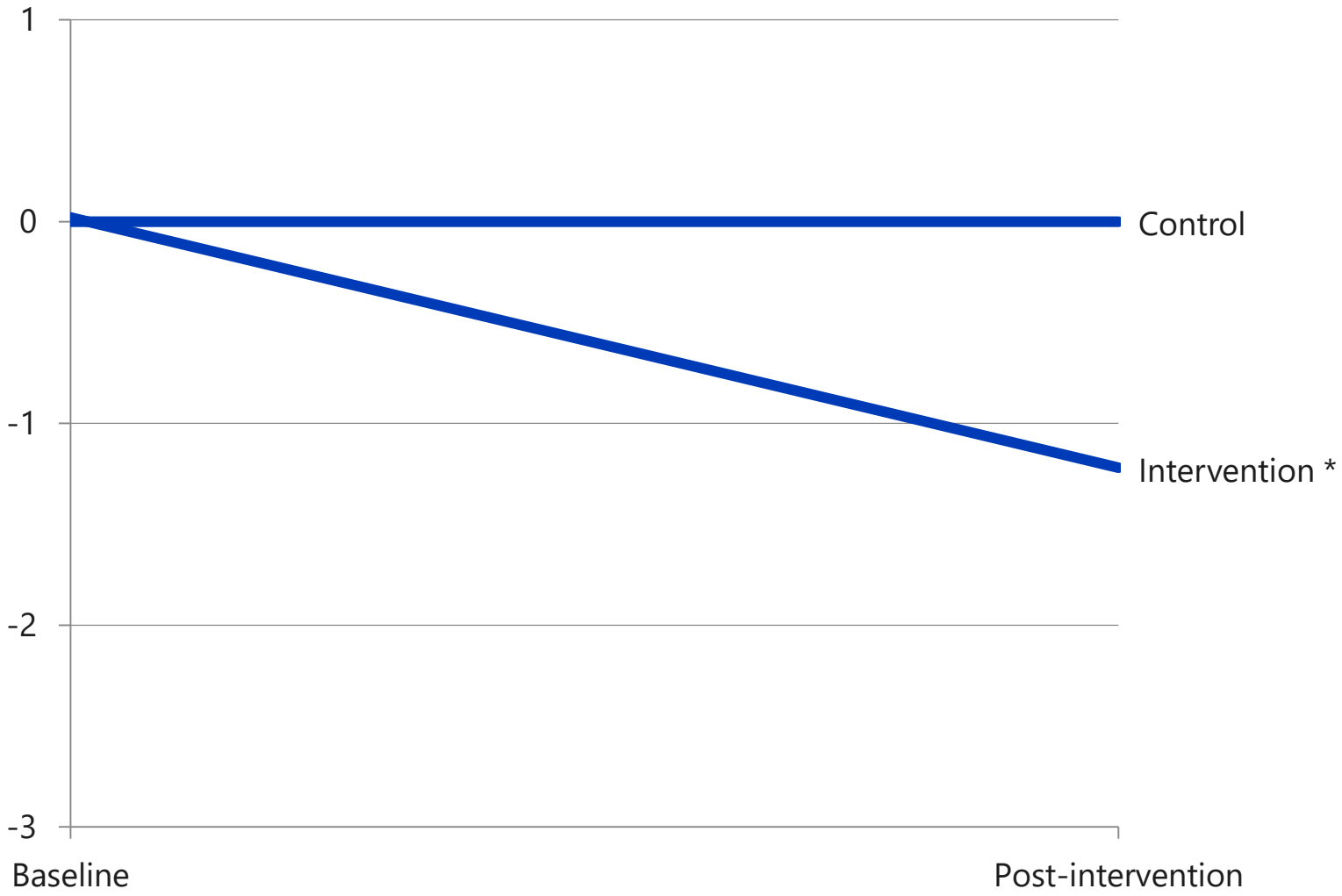


Change in physical activity level
Between baseline to 6-months follow-up
(minutes per week)



Difference in change in physical fatigue (ITT)

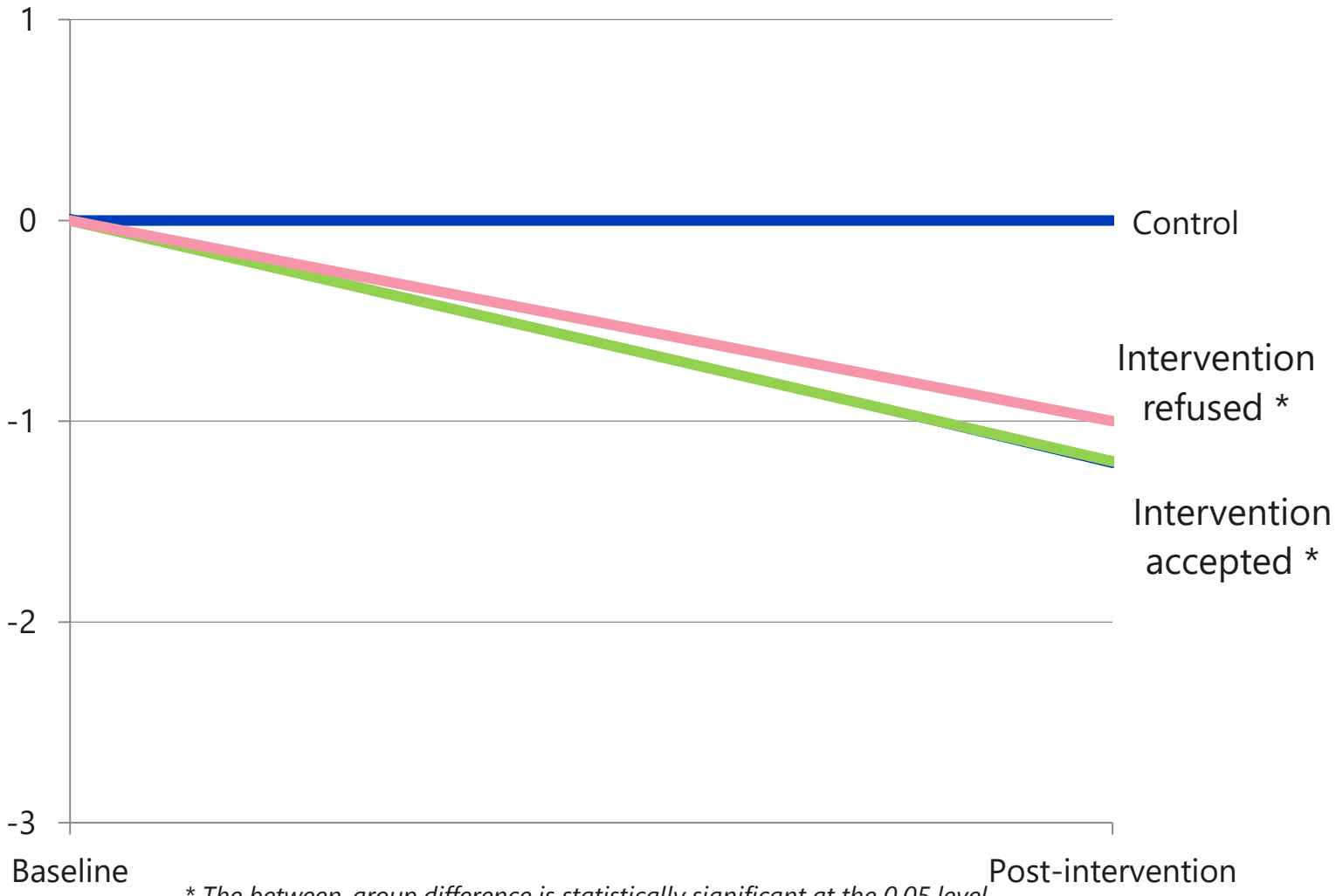
Lower score indicates less fatigue problems



** The between-group difference is statistically significant at the 0.05 level*

Difference in change in physical fatigue (ITT)

Lower score indicates less fatigue problems



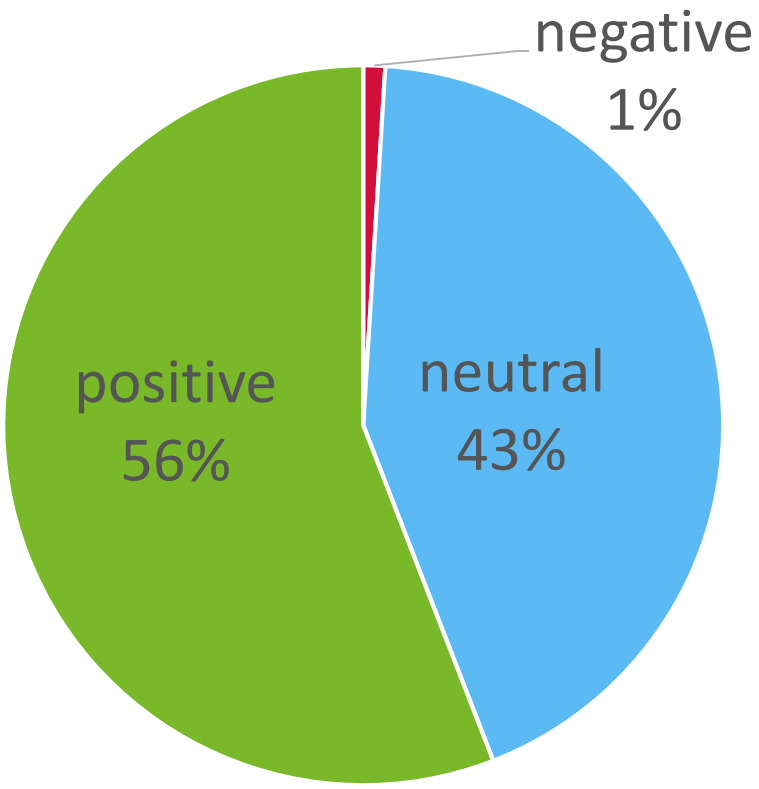
** The between-group difference is statistically significant at the 0.05 level*

TwiCs in clinical oncology: Which advantages have been confirmed?

- Patient-centred informed consent
  - improved recruitment rates ✓
  - more representative sample ✓
- Prevention of contamination ✓

‘How do you feel about having served as a control in a clinical trial without knowing?’

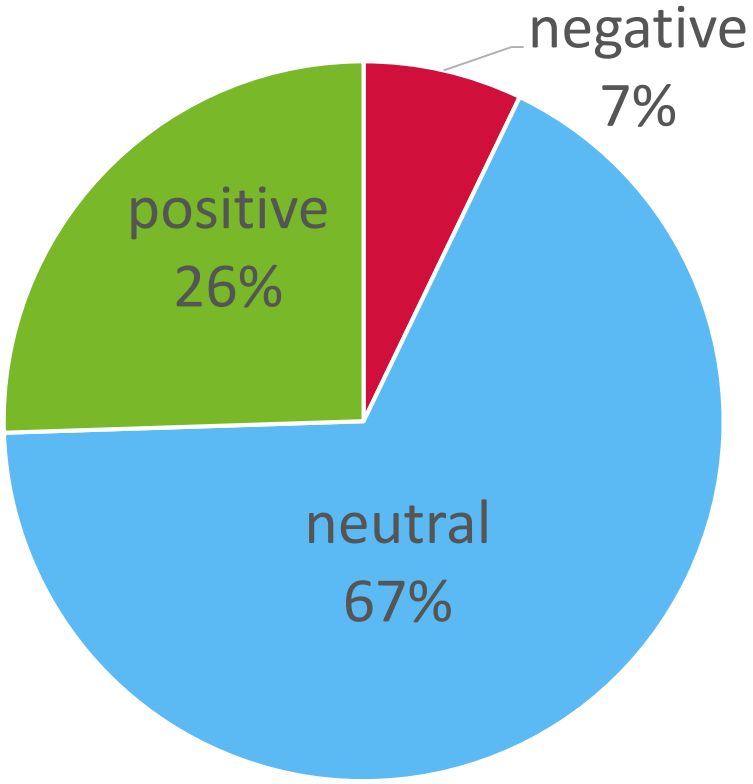
n=102



Verweij et al. In preparation

‘How do you feel about the fact that we did not inform you of being a control in a clinical trial?”

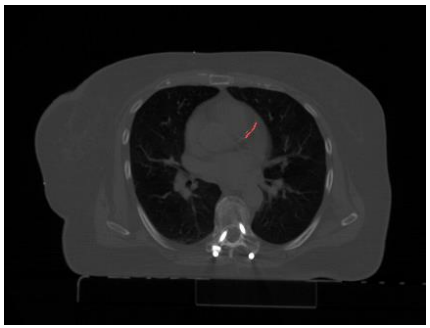
n=98

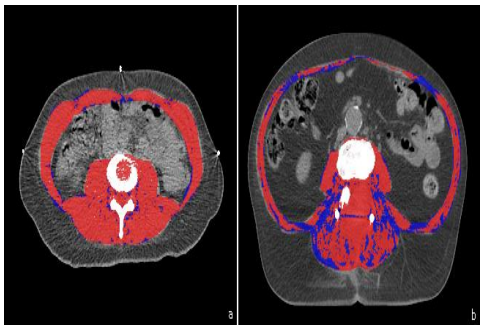


Verweij et al. In preparation

TwiCs in clinical oncology: What have we learnt?

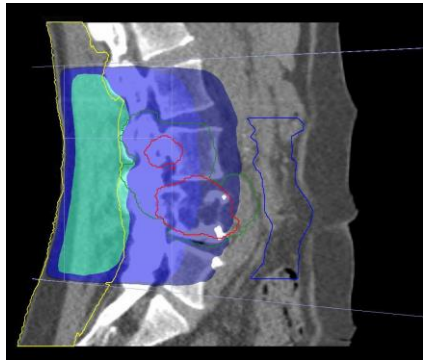
- Staged informed consent is acceptable to patients and IRB's
- Consider sequential or batch randomization
- Non-acceptance and non-compliance depend on intervention
- Be realistic (and not optimistic) about refusal of offered intervention
- Control patients are mostly positive or neutral about being control without further notification.

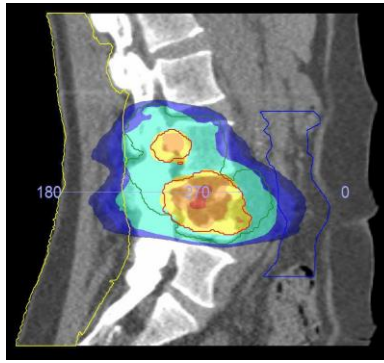


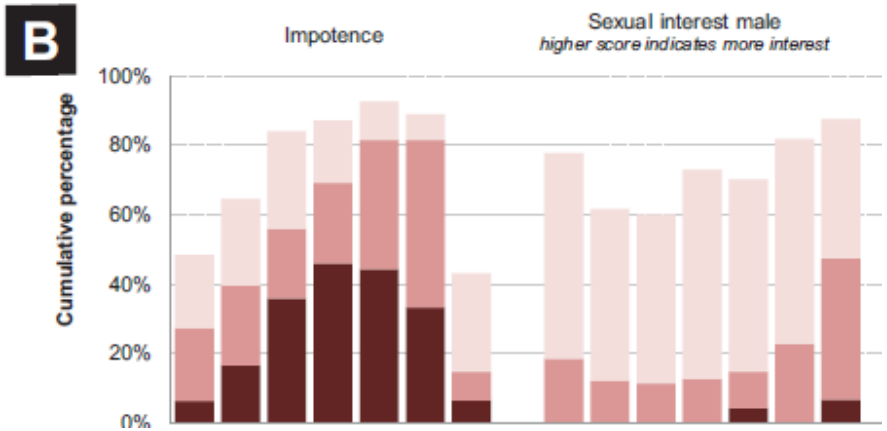


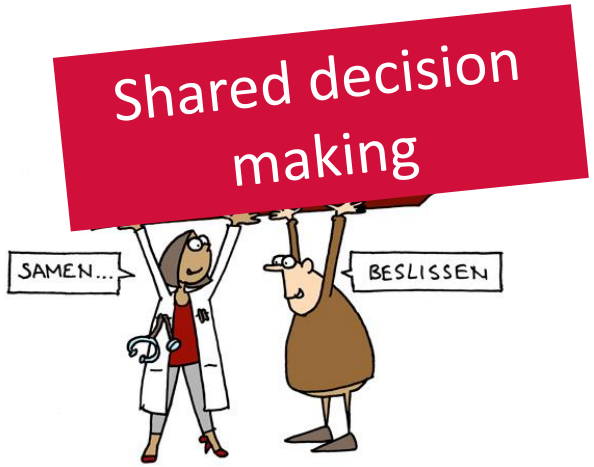
Stereotactic Radiotherapy Followed by Surgical Stabilization Within 24 h for Unstable Spinal Metastases; A Stage I/IIa Study According to the IDEAL Framework

Anne L. Versteeg[1], Joanne M. van der Velden[2], Jochem Hes[2], Wietse Eppinga[2], Nicolien Kasperts[2], Helena M. Verkooijen[2], F. C. Oner[1], Enrica Seravalli[2] and Jorrit-Jan Verlaan[1]









PCTU
Pragmatic Clinical Trials Unit

Thank you

Queen Mary University of London
Barts and The London

Analysis of Trials within Cohorts - Tuesday 25th May
Ethics of Trials within Cohorts - Thursday 27th May

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TRIALS WITHIN COHORTS
FACILITATING MULTIPLE RANDOMISED CONTROLLED TRIALS

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