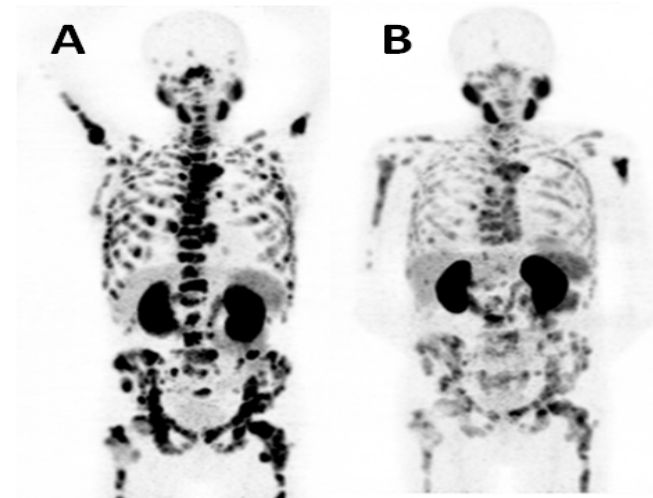
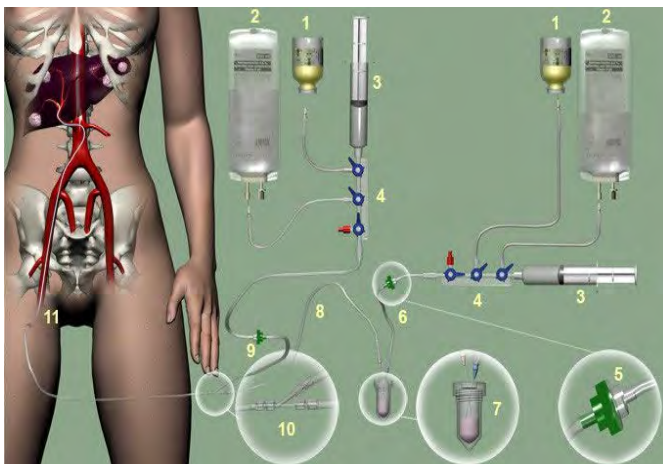
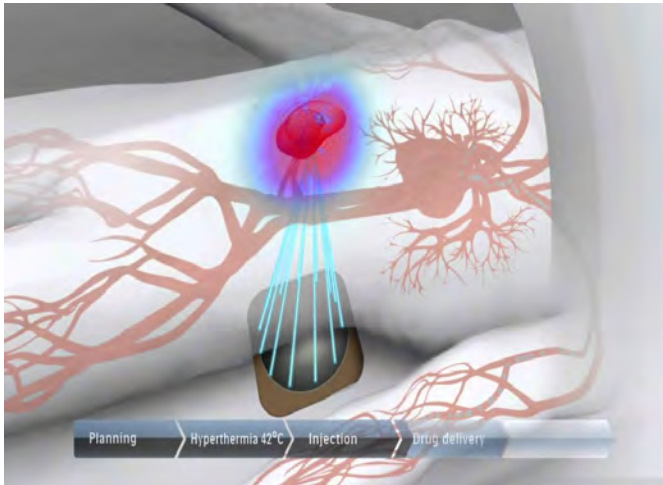


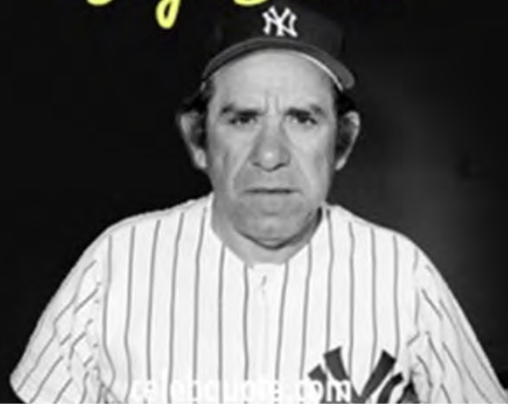
# Abundance of technical innovations in oncology



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IN THEORY THERE IS  
NO DIFFERENCE BETWEEN  
**THEORY** AND **PRACTICE**  
IN PRACTICE THERE IS

*Yogi Berra*



# Classic RCTs are challenging



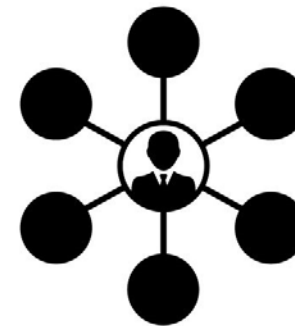
Figure 1 Informed consent – key messages from the patient's perspective.

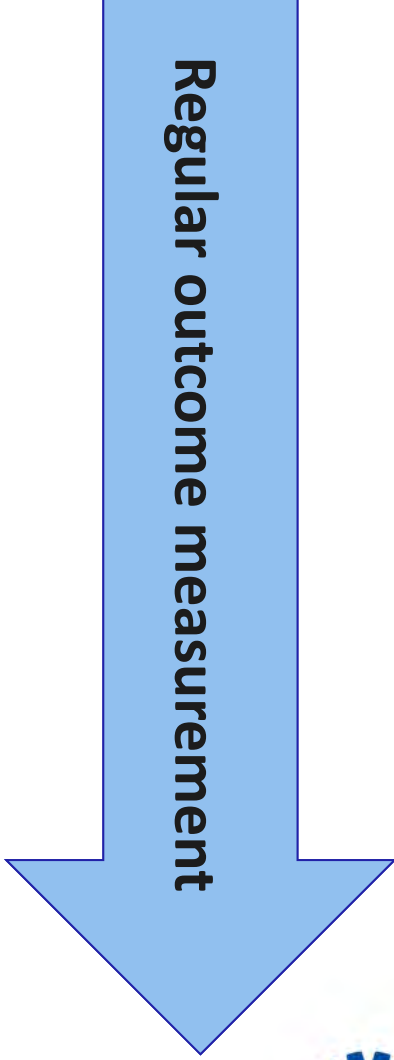
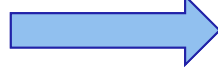
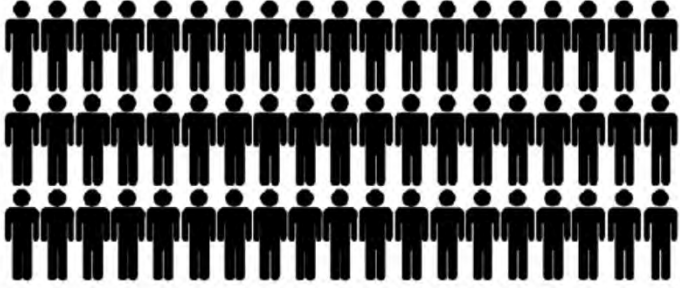


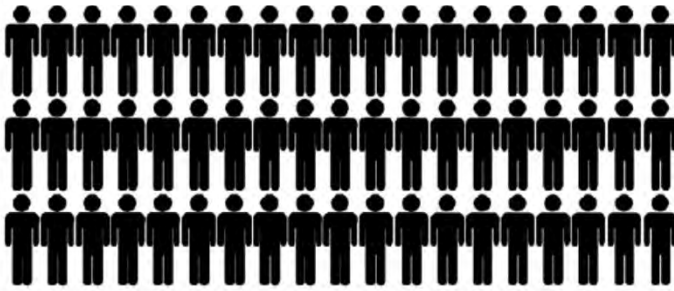
# Classic RCTs in Intervention Oncology face additional challenges



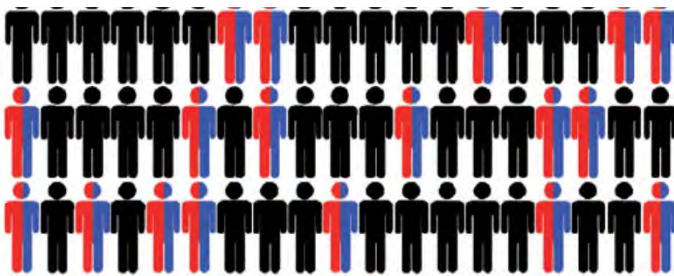
Figure 1 | Informed consent – key messages from the patient's perspective.







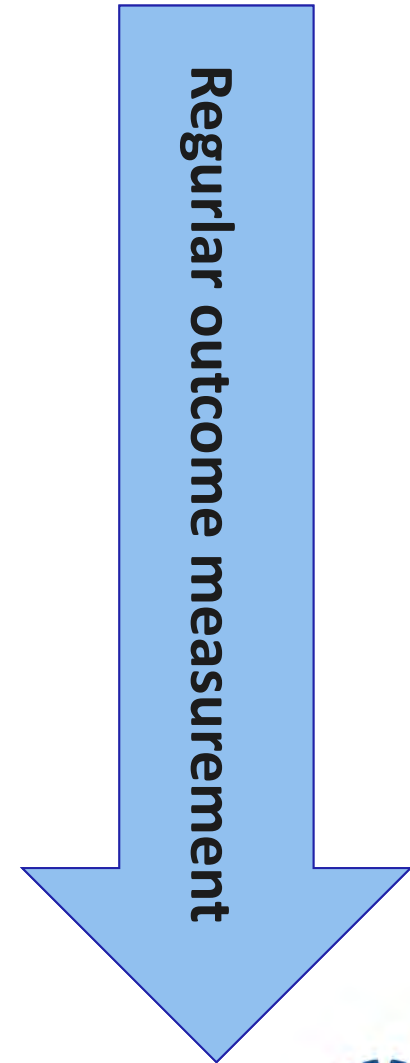
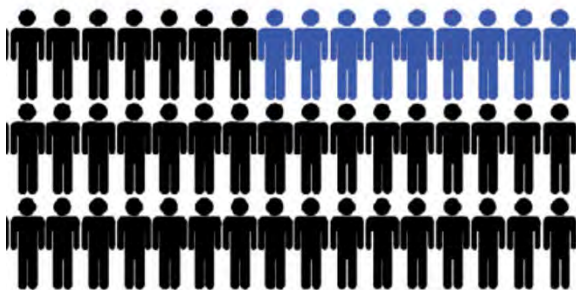
Trial within Cohort  
(TwiCs)



Randomization

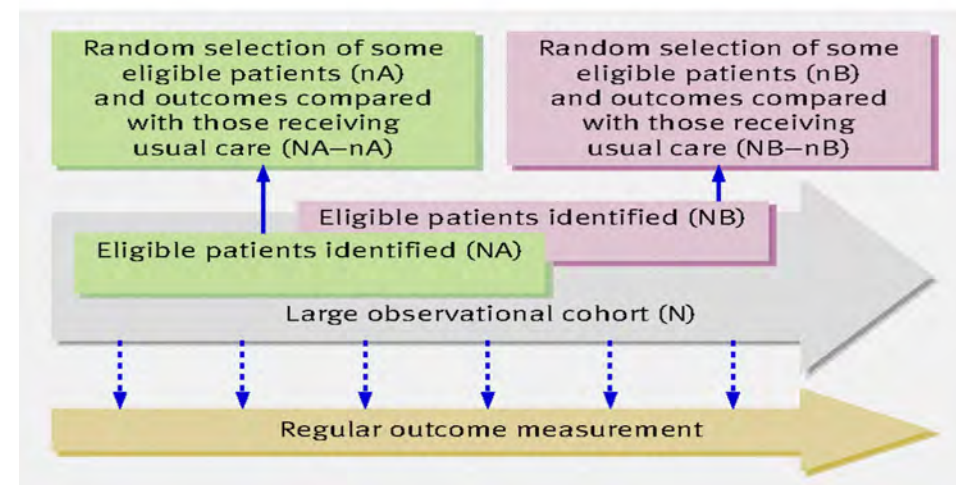
Standard of Care  
(no additional informed consent)

Intervention arm  
(additional informed consent)



# Potential) advantages of TwiCs

- Patient-centred informed consent
  - improved recruitment rates
  - more representative sample
- Prevention of disappointment / contamination
- Facility for multiple RCTs:  
Increased comparability



# 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)







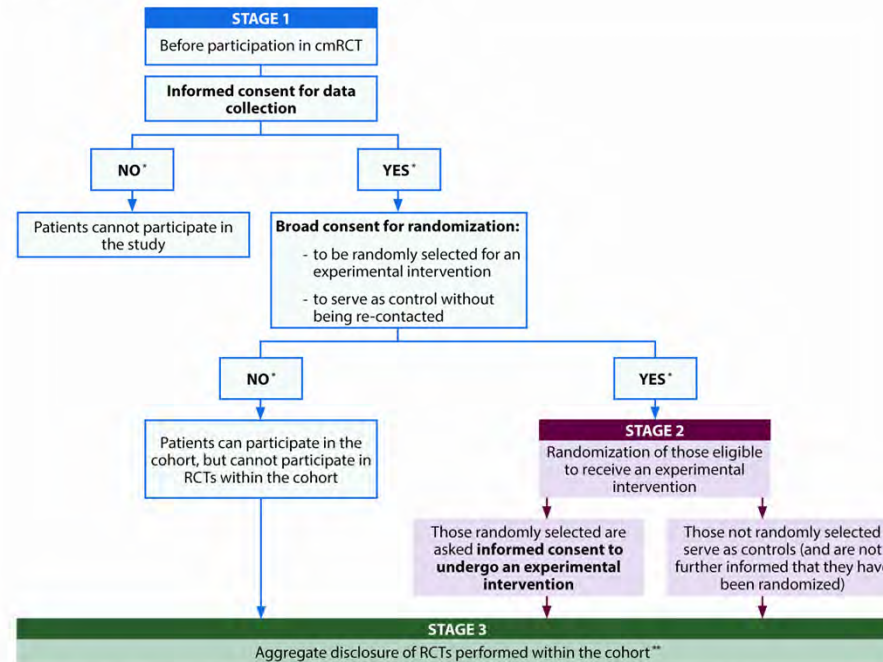
# Staged-informed Consent in the Cohort Multiple Randomized Controlled Trial Design

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

*Epidemiology* • Volume 27, Number 3, May 2016



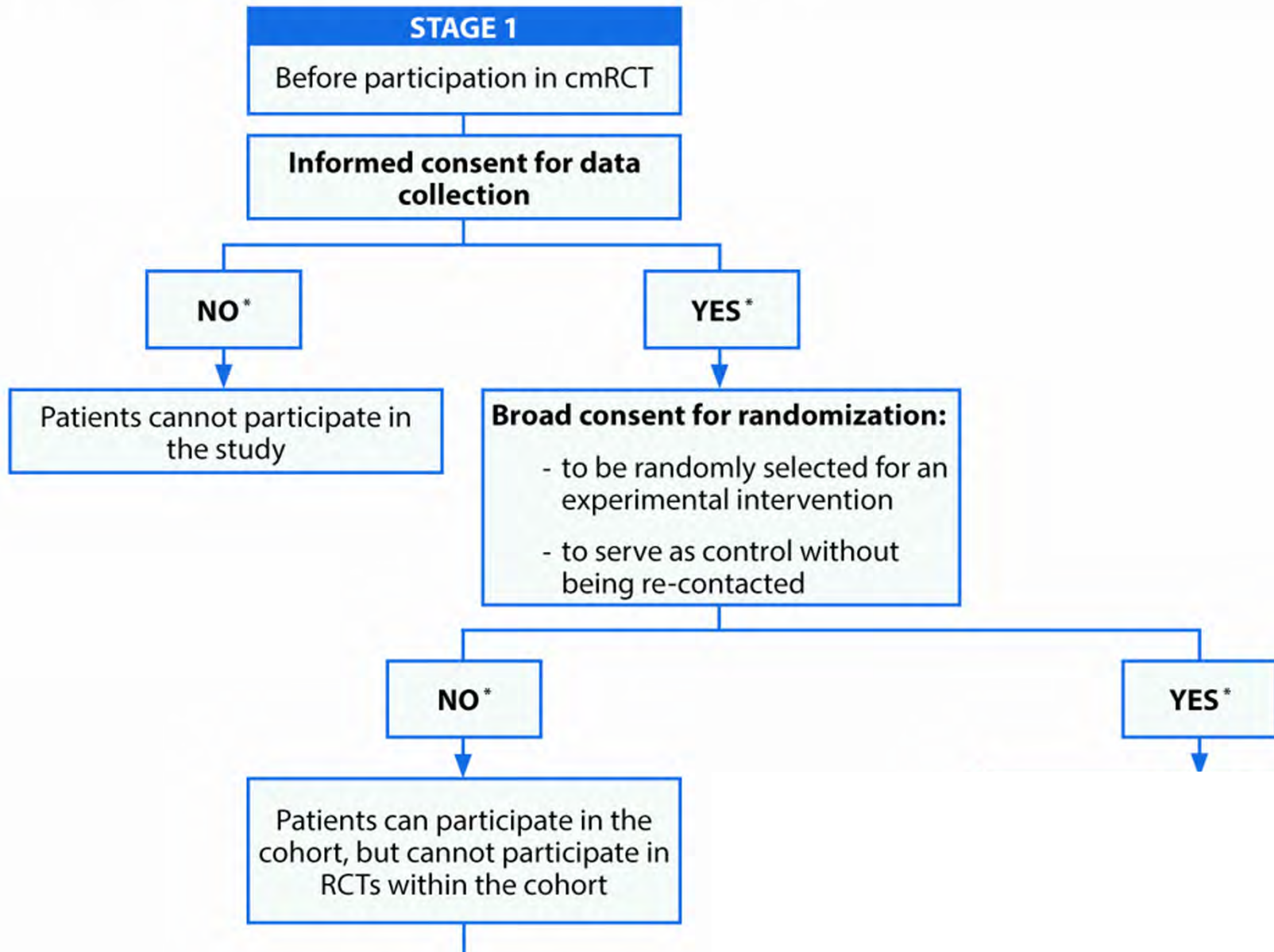
Staged-informed consent model for cmRCT



\*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 aggregate 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)





**STAGE 3**

Aggregate disclosure of RCTs performed within the cohort \*\*

\*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 aggregate disclosure (asked in stage 1).



UNIVERSITY OF TORONTO

# Learn from every patient

## The Innovation Clinic



### Informed consent

Re-use of clinical data



Biobanking



Patient reported outcomes

profiles

Extra scans

### Broad consent for randomization

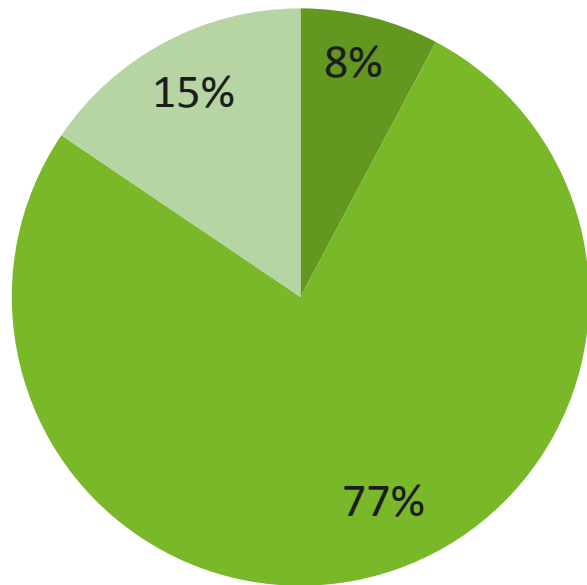


## Our TwiCs infrastructure

Cohort	Site	n	Broad consent for randomization
UMBRELLA	Breast	3150	84%
PLCRC-Urect	Rectal	825	84%
<i>PLCRC</i>	<i>Colorectal</i>	<i>7415</i>	
PRESENT	Bone metastases	1760	82%
OLYMPOS	Lymph nodes	100+	79%
COIMBRA	Brain metastases	75+	69% <i>(75% of patients alive)</i>
UPC	Prostate	15+	
U-Color	Lung	Approved	

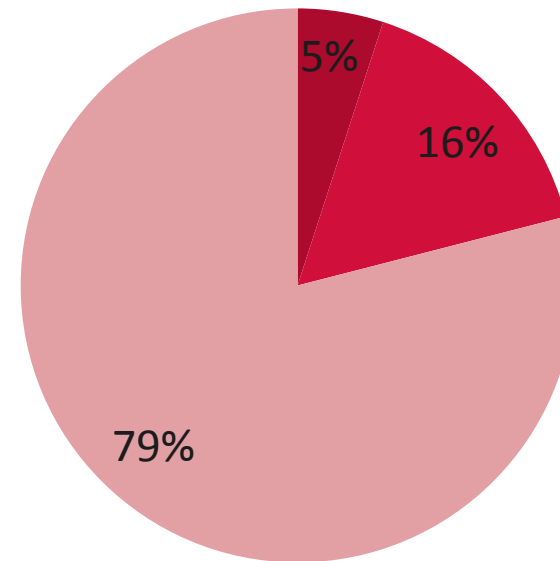
# 'Did you give broad consent for future randomization?'

■ Do not remember ■ Consent ■ No consent



Broad consent given  
N=249

■ Do not remember ■ Consent ■ No consent



Broad consent refused  
N=63



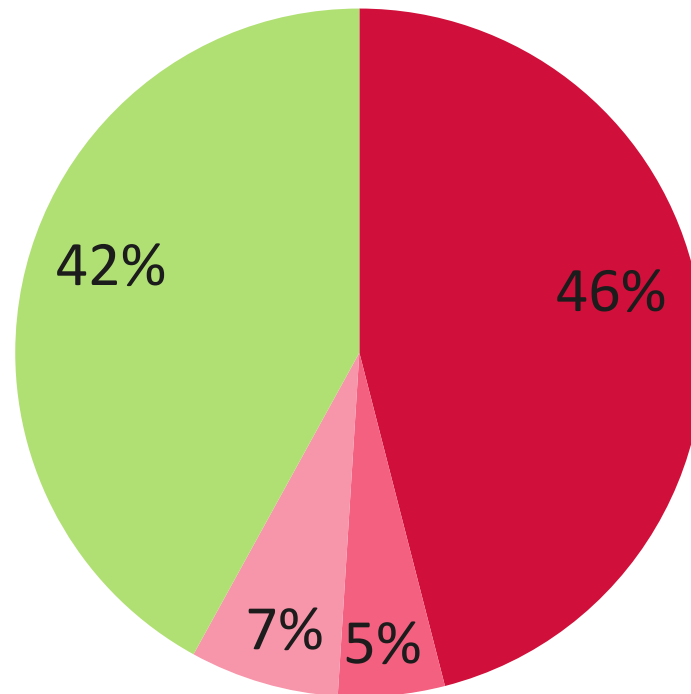
## Trials within Cohorts

Cohort	Site	Randomized trials	Status
UMBRELLA	Breast	<ul style="list-style-type: none"> <li>• Exercise program</li> <li>• Hyperbaric O<sub>2</sub></li> </ul>	<p><b>Completed 260/260</b></p> <p>Recruiting: 39/120</p>
PLCRC	Colorectal	<ul style="list-style-type: none"> <li>• ctDNA guided adjuvant chemotherapy</li> </ul>	IRB submission Jan 2020
PLCRC-Urect	Rectal	<ul style="list-style-type: none"> <li>• Dose escalation</li> <li>• Sponge</li> </ul>	<p><b>Completed: 128/128</b></p> <p>Recruiting : 81/188</p>
PRESENT	Bone mets	<ul style="list-style-type: none"> <li>• Stereotactic radiotherapy</li> </ul>	<b>Completed : 110/110</b>
UPC	Prostate	<ul style="list-style-type: none"> <li>• Nerve sparing RT</li> </ul>	



# 'Do you understand how you have been selected for the experimental intervention?'

N=108



- No, and I don't care
- No, but I would have liked to know
- Yes, I was selected
- Yes, I was allocated by chance (random)

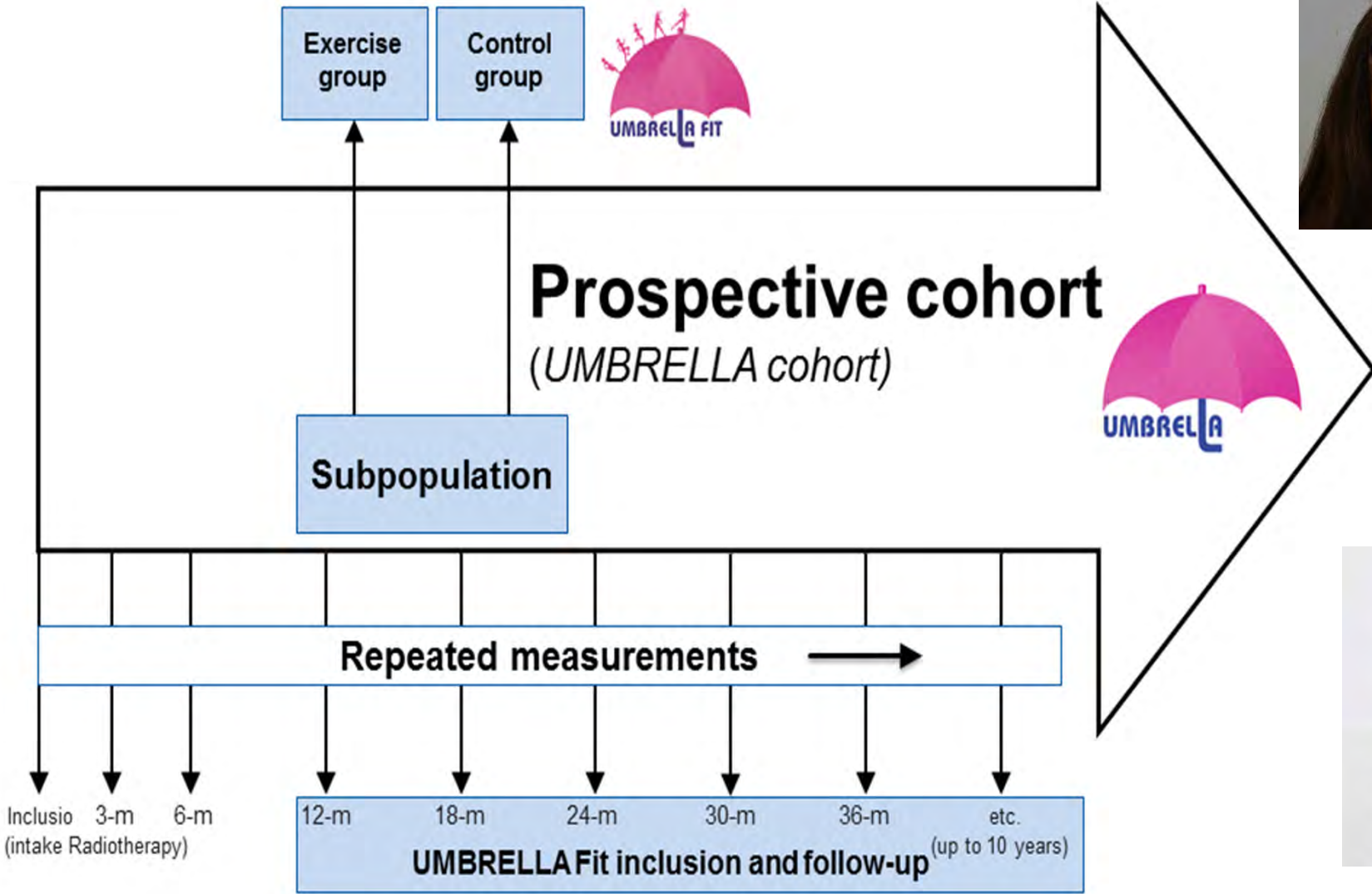


## 3 TwiCs completed

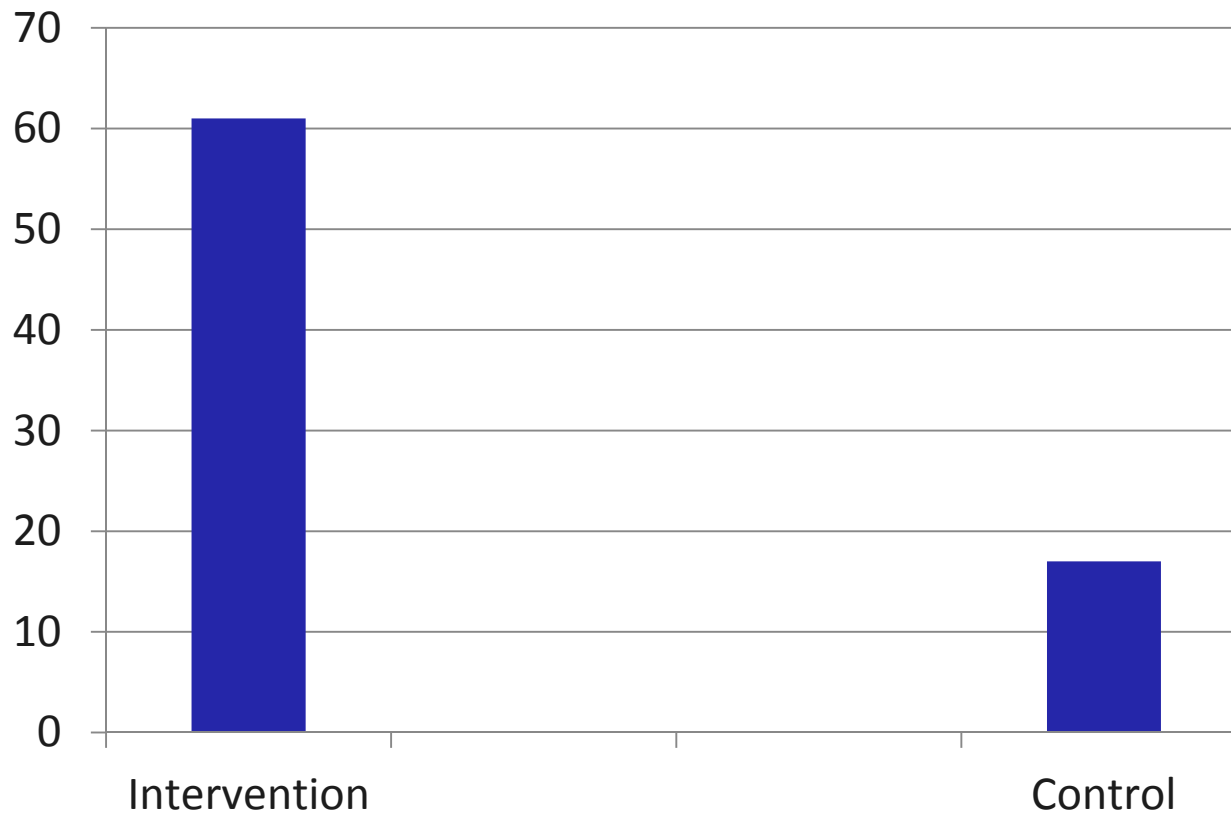
Curative intervention: Radiotherapy dose-escalation

Palliative intervention: Stereotactic radiotherapy

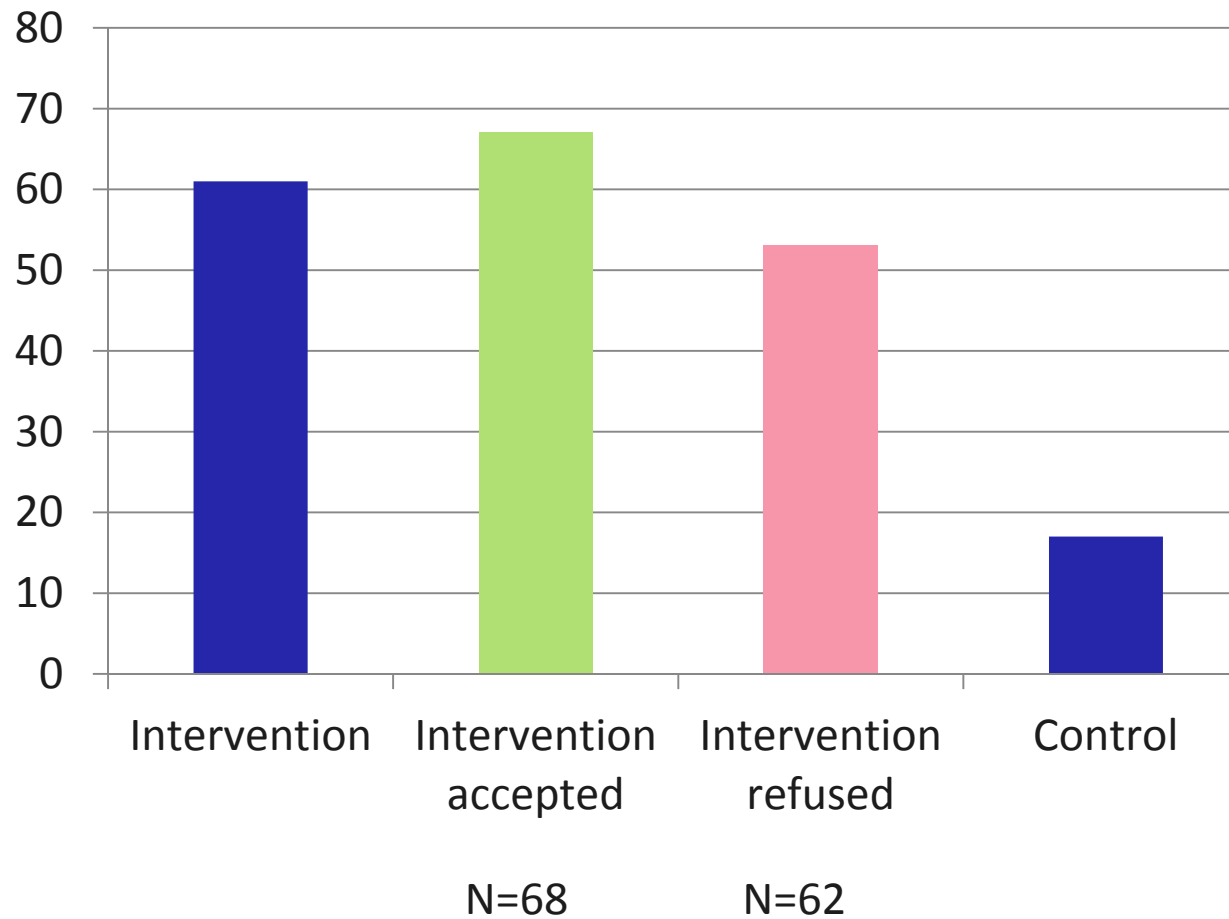
Lifestyle intervention: Exercise program



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

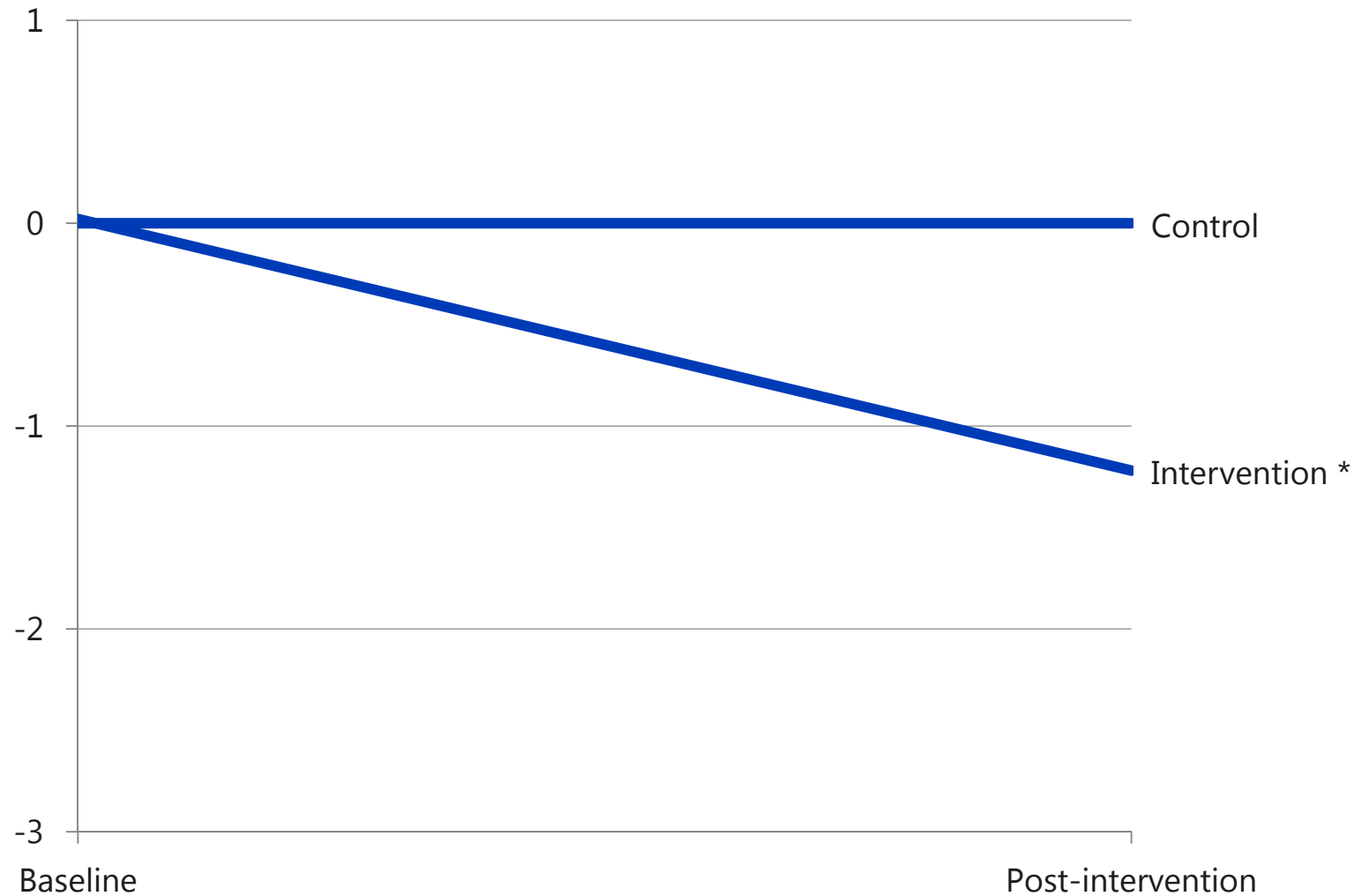


# Change in physical activity level Between baseline to 6-months follow-up (minutes per week)



# Difference in change in physical fatigue (ITT)

*Lower score indicates less fatigue problems*

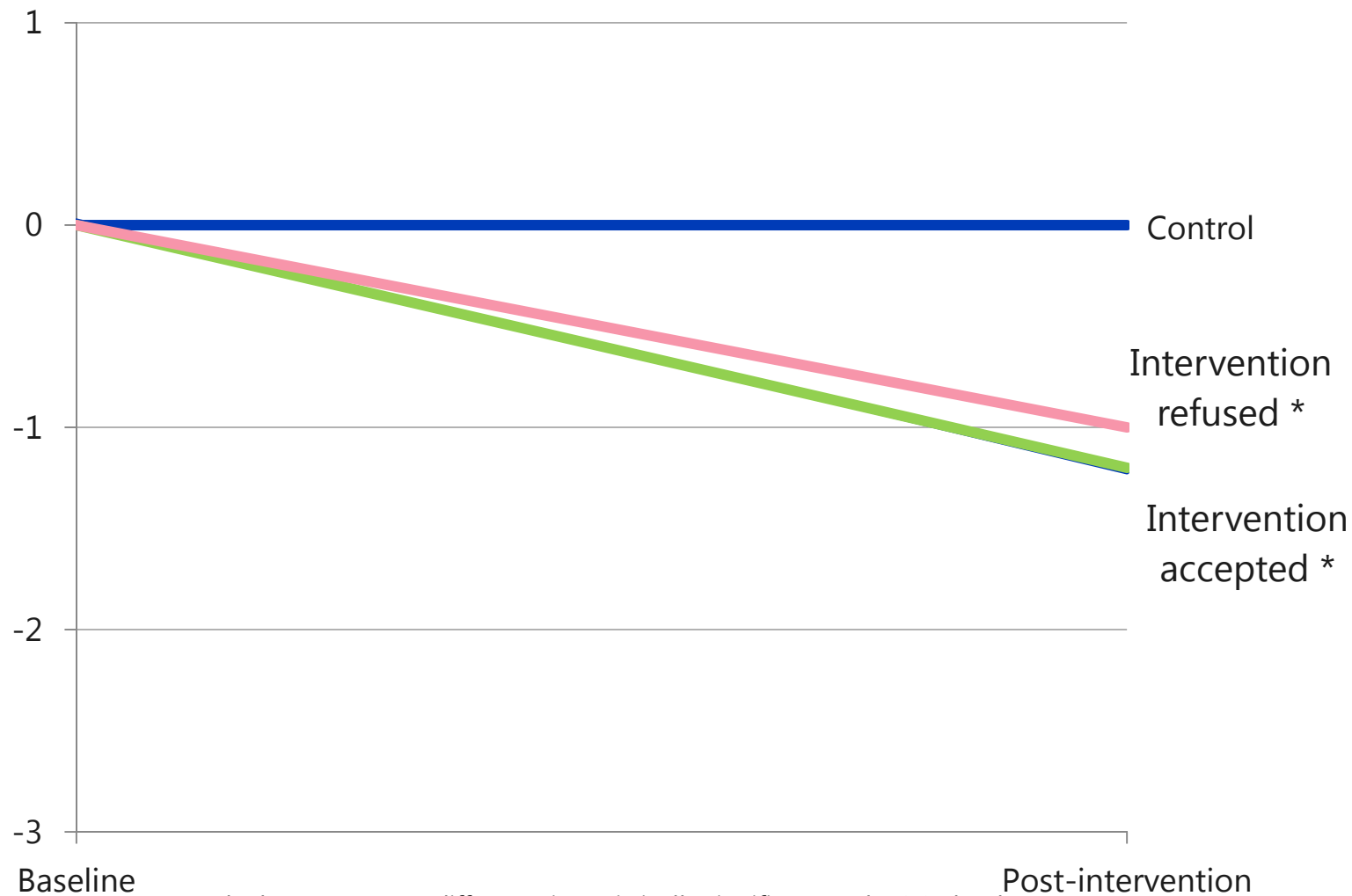


*\* The between-group difference is statistically significant at the 0.05 level*



# 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





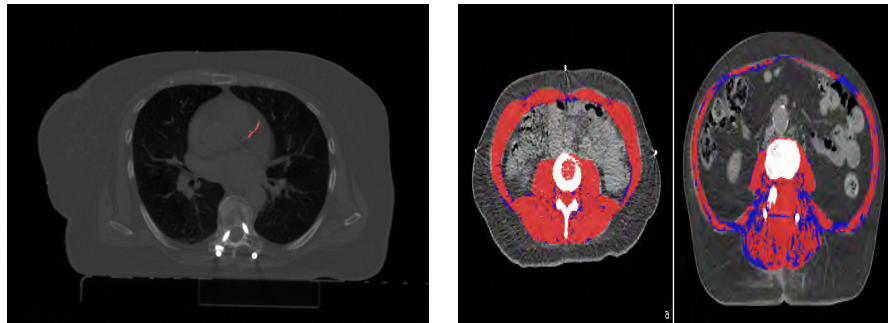
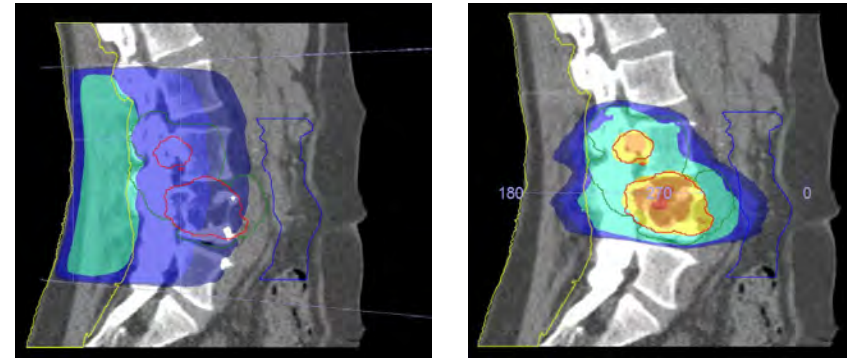
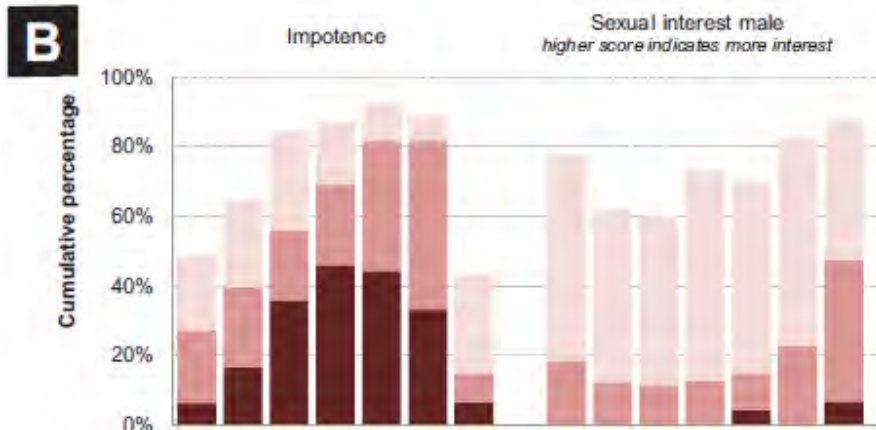
# TwICs in clinical oncology: What have we learnt?

- Staged informed consent is acceptable to patients and IRB's
- Non-acceptance and non-compliance depend on intervention
- Be realistic (and not optimistic) about refusal of offered intervention



# 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<sup>1</sup>, Joanne M. van der Velden<sup>2</sup>, Jochem Hes<sup>2</sup>, Wietse Eppinga<sup>2</sup>, Nicolien Kasperts<sup>2</sup>, Helena M. Verkooijen<sup>2</sup>, F. C. Oner<sup>1</sup>, Enrica Seravalli<sup>2</sup> and Jorrit-Jan Verlaan<sup>1\*</sup>





Innovation! One cannot be forever innovating. I  
want to create classics.

(Coco Chanel)

[izquotes.com](http://izquotes.com)

