Update on statistical considerations

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OPTIMA Investigator meeting 2022

Trial design

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- OPTIMA is a multi-centre partially blinded randomised clinical trial with a **non-inferiority endpoint** of test-directed chemotherapy treatment and endocrine therapy compared to chemotherapy followed by endocrine treatment

- Aims to identify a method of selection that reduces chemotherapy use for patients with hormone sensitive primary breast cancer **without detriment to recurrence and survival**.
- To establish the **cost-effectiveness of test-directed treatment** strategies compared to standard practice

Non-inferiority (NI) trials

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- **Have become more popular since we designed OPTIMA**
- **Used if you are reducing treatment or have new treatment**
  - Could offer important advantages over standard treatment, in terms of
    - Reduction of side-effects
    - Better compliance
    - Less cost
  - whilst being no worse than the standard arm within a pre-set NI margin
- **H_0 (Null hypothesis): The treatments differ**
- **Assess whether there is sufficient evidence to reject the null hypothesis**

Ref Mauri and D'Agostino. Challenges in the Design and Interpretation of Non-inferiority trials. NEJM 2017;377(14):1357-67.

OPTIMA power calculations

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- **Primary endpoint: IDFS**
- **Estimated 5-yr IDFS on standard arm: 85%**
- **Non-inferiority: no worse than 3%* below the estimated 5-year IDFS in the control**
- **1-sided significance: 5%**
- **Power: 85%**

→ Sample size: 4500 pts (2250 in each arm) will have the ability to demonstrate non-inferiority of the experimental arm

* **Prior to trial set-up, consensus from TMG & PPI group : an absolute reduction up to 3% in 5-year IDFS for the test-directed group was acceptable**

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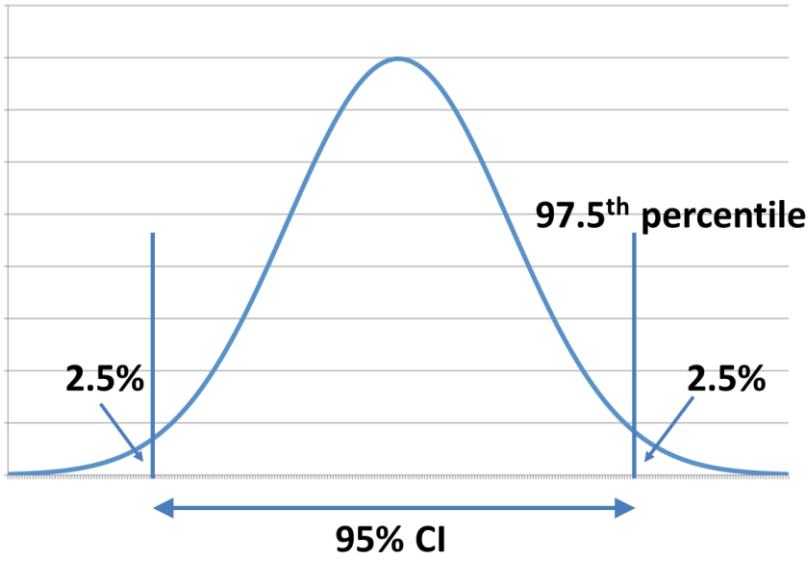
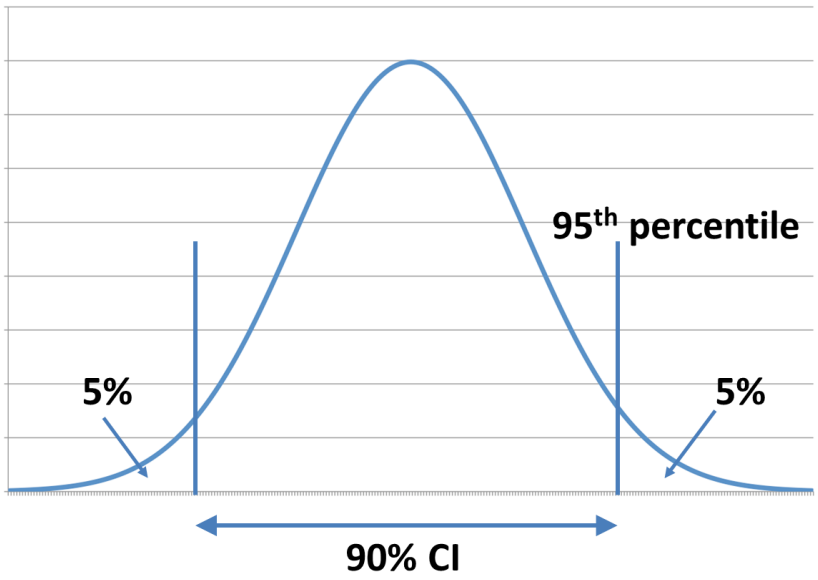
95% CI



90% CI



OPTIMA Primary Endpoint analysis

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- **HR is estimated using a Cox's PH model containing the trial treatment effect**
- **If the 95th percentile (using 90% CI) of the estimated HR is less than the critical value then the experimental arm will be regarded as non-inferior**

5-year DFS on the control arm	3% margin = 3% absolute difference	Critical value (non-inferiority limit)
85%	82%	1.22
88%	85%	1.27
90%	87%	1.32

$=\log_e(0.82)/\log_e(0.85)$

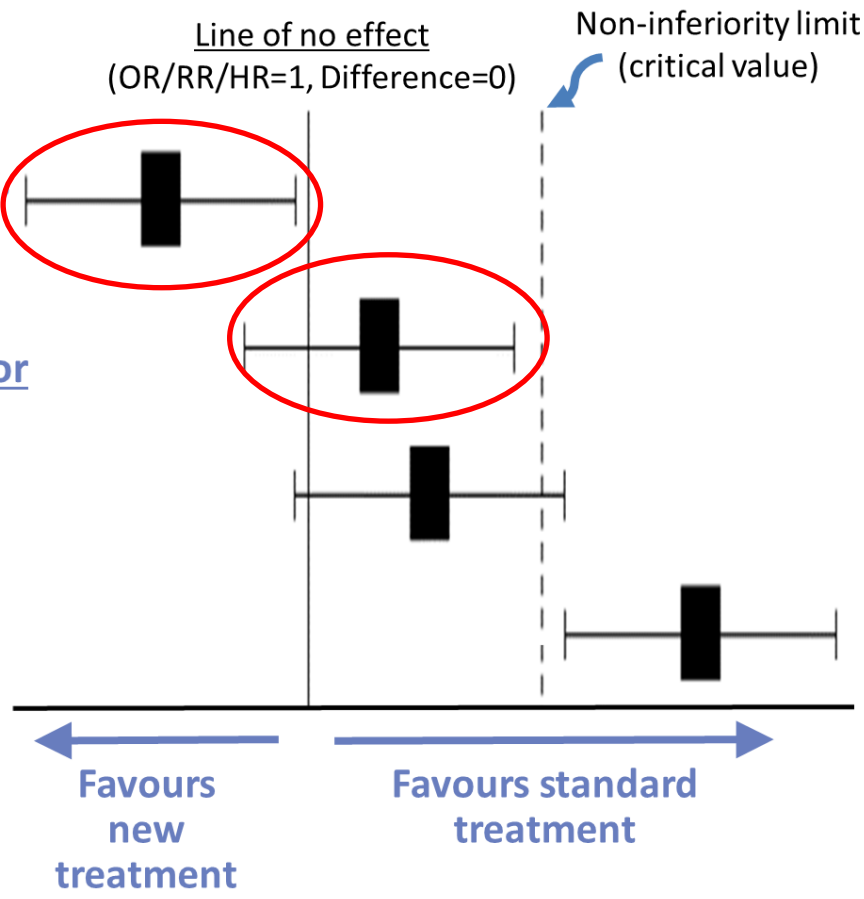
Interpretation of findings

If entire CI < line of no effect, new treatment is **superior**

If upper CI < Non-inf limit, new treatment is **non-inferior**

If upper CI > Non-inf limit, **inconclusive results**

If entire CI > Non-inf limit, new treatment is **inferior**



Current Primary outcome

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- Invasive disease free survival (IDFS):
  - Follows the STEEP definitions and recommendations, decided in 2010.

Outcome measure		Ipsilateral/ regional BC recurrence	Contralateral invasive BC	Distant metastases	Death from BC	Death from other causes	New non-breast cancer
Invasive Disease Free Survival	IDFS	✓	✓	✓	✓	✓	✓

- Unrelated events (new non breast cancers) occur at an increasing rate as patients age during trial follow-up and disproportionally affect those who were older at trial entry. This was found in TAILORx and RxPONDER.
- Risk of false non-inferiority arising from events unrelated to breast cancer (BC).

Proposed new Primary outcome

- Invasive breast cancer free survival (IBCFS):
  - proposed as an alternative to IDFS for non-inferiority trials in STEEP v2
  - Removes non-breast cancers but includes all deaths since attribution of cause is not always accurate.

Outcome measure		Ipsilateral/ regional BC recurrence	Contralateral invasive BC	Distant metastases	Death from BC	Death from other causes	New non-breast cancer
Invasive Disease Free Survival	IDFS	✓	✓	✓	✓	✓	✓
Invasive Breast Cancer Free Survival	IBCFS	✓	✓	✓	✓	✓	X

Secondary outcome measures

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Outcome measure		Ipsilateral/ regional BC recurrence	Contralateral invasive BC	Distant metastases	Death from BC	Death from other causes	New non-breast cancer
Recurrence Free Interval	RFI	✓	X	✓	✓	X	X
Distant Recurrence Free Survival	DRFS	X	X	✓	✓	✓	X
Distant Recurrence Free Interval	DRFI	X	X	✓	✓	X	X
Breast Cancer Specific Survival	BCSS	X	X	X	✓	X	X
Overall Survival	OS	X	X	X	✓	✓	X

Secondary outcome measures

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- Currently the protocol states:
  - Distant recurrence free Interval (DRFI)
  - Distant recurrence free survival (DRFS)
  - Breast cancer specific survival (BCSSS)
  - Overall survival (OS)
- Propose to:
  - Add recurrence free interval (RFI) and IDFS
  - Remove DRFS

ITT versus PP analysis

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- **Intention-to-treat population** includes is all patients randomised irrespective of the treatment received, their eligibility or whether there was inadequate tumour for testing.

- **Per protocol population** includes all patients eligible for trial entry that had their treatment allocated as per the protocol and subsequently followed their randomised trial allocation.

ITT versus PP analysis

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- For superiority trials the ITT population is the gold standard to be used:
  - It preserves balance in randomisation
  - Avoids bias from exclusions
  - Preserves statistical power
  - Conservative and harder to prove superiority
- There is no ‘gold standard’ for the specific population that should be used for non-inferiority trials
- Originally proposed ITT analysis but this has the potential for falsely inferring non-inferiority in the presence of a non-negligible non-adherence to trial allocation.

ITT versus PP analysis

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- Thus the primary analyses will be performed using the per-protocol population.

- To ensure that the results are robust to the choice of population, a sensitivity analysis will be performed on the ITT population.

Specific considerations for the PP populations

Special groups for pp analysis	Include in PP analysis?	Comment
1. Patients ineligible under some protocol versions		
Ineligible when recruited but eligible under final protocol.	Yes	Includes patients who did not meet timelines for study entry & some treated with pre-surgical endocrine therapy.
Patients eligible when recruited but ineligible under final protocol.	No	Small group currently limited to patients with ER 1-10% staining (local pathology).
2. Patient eligibility potentially affected by laboratory issues post-randomisation		
Patients who are otherwise eligible, but Prosigna testing cannot be completed.	Yes	This group are allocated chemotherapy irrespective of randomisation according to the protocol.
Patients with Prosigna classified non-luminal tumours and subsequently found ineligible by central receptor confirmation.	Yes	Strictly these are not per protocol as treatment was not allocated by protocol. Removal of this group however would only affect the test-directed arm as an equal number of these patients will be undiscovered in the control arm.

Specific considerations for the PP populations ctd

Special groups for pp analysis	Include in PP analysis?	Comment
3. Patients not treated in accordance with protocol.		
Patients allocated CT who did not receive at least 1 cycle	No	These are patients who declined their allocated treatment or who were not treated for other reasons.
Patients allocated endocrine therapy who were treated with CT	No	These are patients who declined their allocated treatment or who were treated with chemotherapy for other reasons.
Patients who did not commence or who discontinued endocrine therapy early	Yes	Significant numbers of patients discontinue endocrine therapy and a few decline treatment entirely. This is a real world situation; there is no reason to exclude such patients.

Power calculation

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- Changing the primary outcome from IDFS to IBCFS will increase the power if all other assumptions stay the same
- Changing from ITT and including all patients to a per protocol analysis will reduce the power as will be analysing less patients

Power calculation

Scenario	Rate for control at 5 years	Non-inferiority margin	HR CV	Minimum Sample size in each arm	Recruitment period in months	Minimum additional follow-up in months	Power
Original	85%	3%	1.22	2250	48	36	85%
Current	85%	3%	1.22	2250	60	21	77%
Scenario A	85%	3%	1.22	2250	96	12	81%
PP 5%	85%	3%	1.22	2137	96	12	80%
ITT	86%	3%	1.235	2250	96	12	84%
PP 10%	86%	3%	1.235	2025	96	12	81%
ITT	87%	3%	1.252	2250	96	12	85%
PP 10%	87%	3%	1.252	2000	96	12	82%
ITT	88%	3%	1.271	2250	96	12	87%
PP 10%	88%	3%	1.271	2025	96	12	85%
PP 15%	88%	3%	1.271	1913	96	12	80%
ITT	89%	3%	1.294	2250	96	12	89%
PP 10%	89%	3%	1.294	2025	96	12	86%
PP 15%	89%	3%	1.294	1913	96	12	84%
ITT	90%	3%	1.322	2250	96	12	91%
PP 10%	90%	3%	1.322	2025	96	12	88%
PP 15%	90%	3%	1.322	1913	96	12	86%

Pre-planned analyses

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- Key secondary analysis (patients with low-score tumours) across all efficacy endpoints for these patients
- The chemotherapy effect on ER-positive disease declines steadily over time, the effect on the hazards over time will be investigated
- Exploratory analyses will be undertaken within pre-defined subgroups of particular interest, specifically menopausal status, extent of nodal involvement and tumour grade, which are stratification factors

Conclusions

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- Proposed changes to primary outcome from IDFS to IBCFS and from and ITT to a PP analysis are trying to mitigate the chances of falsely inferring non-inferiority
- These proposed changes will be made to the protocol and subsequently in the SAP
- We will keep an eye on the statistical power