Impact of the SARS-CoV-2 Pandemic on the Conduct of DCP Trials:

Update on TMIST – Tomosynthesis Mammographic Imaging Screening Trial

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Introduction

- The pandemic has decreased accrual to our trials.
- As some of these trials take a long time to complete, it is important to ask if these trials are still poised to answer the critical research questions they were intended to address in a timely fashion.
- We consider on-going reviews of our prevention trials as our stewardship responsibility.
- Today I would like to focus on TMIST, DCP’s largest trial.
Primary Aim and Summary of TMIST

- To determine whether the cumulative rate of advanced breast cancer in women undergoing screening with tomosynthesis plus digital mammography (“3-D”) is reduced compared to digital mammography (“2-D”) alone.
- Advanced cancer is defined as any cancer diagnosed in the 4.5 years after study entry that is metastatic or a large tumor (based on subtype).
- Mortality is not the endpoint of TMIST.
- TMIST is being conducted at NCORP and non-NCORP sites and is being led by Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN) (ECOG-ACRIN).
- TMIST was originally projected to complete enrollment by 2020 (2.5 years of accrual) (5,500 per month) and to finish in 2025.
- Proposed Sample Size = 165K participants; current enrollment is <30K
- Estimated Costs for 2021-4: $93.9 Million
Study Design

**TMIST Cohort:**
Women Ages 45 - 74 Presenting for Breast Screening (N = 165,000)

- Consent/Registration
- Randomization

**Randomization**

**DIGITAL MAMMOGRAPHY (DM)**
**TOMOSYNTHESIS (TM)**

- Screening Annually\(^1\) (Baseline, 12-, 24-, 36-, 48- Months), Biennially\(^2\) (Baseline, 24-, 48- Months) or Until Cancer Detected

- **NEGATIVE SCREEN**
  - Continue Screening per Study Schedule

- **POSITIVE SCREEN**
  - Diagnostic Imaging
  - Biopsy

  **Positive**
  - Tissue/Slide Collection

**Follow-up:** Patients are followed for a maximum of 8.0 years after study entry

**Cancer Diagnosis & Local Tx Decision Making**
Clinical Sites

- 112 sites are currently open to accrual in CTSU
- 99 sites have enrolled at least 1 participant
- 13 sites are currently open in CTSU but have no enrollments as of 9/1/2020
- 23 US sites and 3 international sites are in the process of submitting qualifications to activate TMIST
Accruals and the Impact of COVID

To Date:

- **Target Accrual**: 165K (Average ~5,500 per month) (completion of enrollment)
- **Actual Accrual**: <30K (Average <1,500 per month)
  - Maximum enrollment of ~1,700 (January & February of 2020)
  - Impact of COVID: ~50% reduction in enrollment (vs. 1,700 per month) for a 6-month period from March through August

*TMIST Activation on July 6, 2017; 1st Accrual on September 28, 2017*
Summary of the Evidence

- **Meta-Analysis by Marinovich *et al.*, JNCI, 2018:
  - *Single-Arm Studies*. 3-D detected more cancers but had a marginally higher recall compared to 2-D; and
  - *Two-Arm Studies (RCTs)*. 3-D detected more cancers and had a lower recall compared to 2-D

- **Observational Study by Lowry *et al.*, JAMA, 2020:
  - 3-D detected more total and invasive cancers, resulted in more biopsies, but had fewer recalls than 2-D; and
  - 3-D had a lower recall-to-cancer and biopsy-to-cancer ratios compared to 2-D
## Landscape Analysis of Ongoing Trials (from clinicaltrials.gov)

<table>
<thead>
<tr>
<th>NCT</th>
<th>Study Title</th>
<th>N; Age Range (Years)</th>
<th>Start-End</th>
<th>Follow-Up</th>
<th>Locale</th>
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<tbody>
<tr>
<td>03377036</td>
<td>Breast Cancer Screening: Digital Breast Tomosynthesis Versus Digital 2D Mammography</td>
<td>80,000; 50-69</td>
<td>07/18-07/23</td>
<td>2 Years</td>
<td>Germany</td>
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<tr>
<td>03733106</td>
<td>Prospective Trial of Digital Breast Tomosynthesis (DBT) Breast Cancer Screening</td>
<td>100,000; 50-70</td>
<td>12/18-07/24</td>
<td>3 Years</td>
<td>UK</td>
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<tr>
<td>02835625/6</td>
<td>The Digital Breast Tomosynthesis Trial in Bergen - Part 1 &amp; 2</td>
<td>~30,000; 48-71</td>
<td>01/18-01/22</td>
<td>2 Years</td>
<td>Norway</td>
</tr>
</tbody>
</table>
Key Considerations:

- Under-accrual, compounded by the SARS-CoV-2 pandemic, will likely result in delayed outcomes and escalate costs; ECOG-ACRIN is adding sites but it is unclear if a 3,000-per-month accrual ever will be achieved (n.b., 2,000 per month has never been achieved).

- Relevance of the data by the completion of the trial is uncertain because:
  - 3-D market penetrance by the conclusion of the trial (68% of Certified Facilities have at least one 3-D Unit and 40% of all units are 3-D in 2020); and
  - Evidence is already available suggesting that 3-D is no worse and probably better than 2-D; and
  - Other trials and observational cohorts, while imperfect, will contribute additional, informative data.
Final Comments & NCAB Advice Sought

- As initially conceived, TMIST will not complete accrual until 2023 (if 3,500 enrolled per month) or 2026 (if 2,000 enrolled per month)(vs. mid-2020 completion). There could be further delays if there is a long-term impact of the pandemic.

- Follow-up (~5 years) and primary data analysis (~1 year) will add ~6 years after enrollment i.e., completion and reporting of the data between 2029 and 2032 (vs. 2025).

- Ongoing breast cancer screening trials will report their results well before then, and radiological practice likely will change substantially during that interval.

- We propose the creation of Working Group, reporting to Clinical Trials and Translational Research Advisory Committee, to examine the utility of TMIST given these unanticipated challenges due to the pandemic.