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Authors: Andrew Coldman, Joy Pader, Cynthia Gauvreau, Saima Memon, Natalie Fitzgerald, William Flanagan, Claude Nadeau, Craig Earle, Michael Wolfson, Anthony Miller, Jason Lacombe

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# Simulating Results from Trials of Sigmoidoscopy Screening

# Using the OncoSim Microsimulation Model

Andrew Coldman[1] PhD, Joy Pader[2] MPH, Cynthia Gauvreau[2] PhD, Saima Memon[2] MPH, Natalie Fitzgerald[2] MSc, William Flanagan[3] BM, Claude Nadeau[3] PhD, Craig Earle[4] MD, Michael Wolfson[5] PhD, Anthony Miller[6] MD, Jason Lacombe[7] MSc

[1] - BC Cancer Research Centre, Vancouver, BC

[2] - Canadian Partnership Against Cancer, Toronto, ON

[3] - Statistics Canada, Ottawa, ON

[4] – Ontario Institute for Cancer Research, Toronto, ON

[5] – University of Ottawa, Ottawa, ON

[6] – University of Toronto, Toronto, ON

[7] - University of Oxford, Oxford, UK

Short Title: Simulating Sigmoidoscopy Screening Trial Results

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[*]Corresponding Author: Andrew James Coldman, BC Cancer Research Centre, 675 W 10th Ave, Vancouver, BC. V5Z 1L3 CANADA Tel #: 604-219-9443, Fax: 604-224-3529 acoldman@bccrc.ca

## HIGHLIGHTS

- Four RCTs of CRC screening sigmoidoscopy were reviewed
- The OncoSim model was able to simulate the results of the four RCTs
- Predicted reductions in CRC incidence and mortality agreed with observations
- These results validate OncoSim CRC natural history and screening assumptions

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**ABSTRACT**

**Introduction:** Projection of the effect of cancer screening interventions are frequently conducted using complex simulation models. It is important that such models demonstrate their ability to replicate observational results on the effect of screening. We present results using the OncoSim-CRC microsimulation model to replicate results from four randomized trials (RCTs) of sigmoidoscopy screening for colorectal cancer (CRC).

**Methods:** The published results of four RCTs of sigmoidoscopy were reviewed. Two key outcomes were identified: the intention-to-treat hazard ratios (HR) for CRC incidence and CRC mortality for the screening versus control arms. Each RCT study arm was simulated within OncoSim-CRC using the study specific entry criteria, follow-up and observed participation and compliance rates. The ratio of predicted cases (deaths) between intervention arm and control arm was used to estimate the HRs.

**Results:** The RCTs differed in the implementation of sigmoidoscopy screening and only one (PLCO) used more than one cycle. All four RCTs found significant reductions, HR<1, in CRC incidence (range 0.77-0.82) and three for CRC mortality (range 0.69-0.78). The four study cohorts were successfully simulated to match the age and sex structure and length of follow-up of the study cohorts. Each OncoSim-CRC trial-specific predicted reduction fell within the confidence intervals for the observed HR for CRC incidence and CRC mortality for the corresponding trial. The predicted ranges of HRs for incidence was 0.74-0.82 and for mortality was 0.66-0.76 for the four trials.

**Conclusions:** OncoSim-CRC predicted reductions in CRC incidence and mortality agreed well with observed in RCTs of sigmoidoscopy screening.

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Keywords:

Colorectal cancer, screening, sigmoidoscopy, microsimulation model, validation

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## INTRODUCTION

Sigmoidoscopy has attracted much interest as a screening tool for the early detection of Colorectal Cancer (CRC) and precursor adenomas (1,2). Sigmoidoscopy has the advantage of direct examination of the distal colon and rectum and compared to colonoscopy, sigmoidoscopy is less invasive and may be performed more rapidly and by non-physician operators. Approximately 65% of CRC occur in the rectum or distal colon (3) and discovery of a distal polyp may result in a colonoscopy being recommended depending upon the management strategy followed. Four randomized trials (RCT) have reported results of sigmoidoscopy screening (4-7) along with many non-randomized studies (8). Three of the RCTs were conducted in Europe - UK Flexible Sigmoidoscopy Trial (UKFS), Screening for Colon Rectum (SCORE) and Norwegian Colorectal Cancer Prevention Screening Study (NORCCAP) - and one in the USA, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO).

Although sigmoidoscopy represents an attractive option for screening for CRC, other options exist. Fecal occult blood, both guaiac based (FOBT) (9,10) and immunochemical tests (FIT) (11), as well as colonography (12) and colonoscopy (8) are used in different jurisdictions. Furthermore, options include decisions about whether to use a single modality or a combination (13), how frequently to test and the definition of eligible subjects. The multiplicity of potential options, and the time-span over which the effects of screening are operative, imply that randomized trials can provide an evaluation of only a limited number of possibilities. Consequently, quantitative models incorporating the natural history of CRC development, screening, treatment and outcomes are used to make projections about the effects of different screening scenarios. One such model is the OncoSim-CRC (formerly called the Cancer Risk Management Model or CRMM) (14) which is a dynamic population model for CRC calibrated to

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Canadian cancer incidence, staging and mortality up to 2008 and utilising costs of care from Canadian sources.

Quantitative models typically utilize data from diverse sources and are calibrated against a variety of disease targets (15). Where possible, model predictions should be compared to the outcome results of randomized control trials of cancer screening to show that the model provides appropriate predictions of benefit in situations where the outcome is known (16,17). OncoSim-CRC was developed before long term follow-up results from the trials of sigmoidoscopy were available and we present here the results of using OncoSim-CRC to predict the results of four published RCTs of sigmoidoscopy.

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## METHODS

The four trials of sigmoidoscopy screening have published descriptions of methods and design (4-7). Publications from the trials were reviewed and details of the designs, disease management strategies and cohorts enrolled extracted. Similarly, published follow-up results of the trials were reviewed and outcomes extracted. Primary outcome measures selected were the hazard ratio of CRC diagnosis and the hazard ratio of CRC death comparing the screening to referent arms in each of the trials.

OncoSim-CRC (version 2.3) was used to simulate the results of the trials. OncoSim-CRC is available on a publicly accessible website to registered users (18). Details of the OncoSim-CRC model have been published (14). In its default settings, OncoSim-CRC reflects the status quo of colorectal cancer health outcomes, having been calibrated to observed results in the Canadian population, and of the patterns of screening and treatment in Canada. In this analysis the base, default parameters for the natural history of CRC in OncoSim-CRC were used, i.e. no parameter values were adjusted for this analysis. Similarly, parameters reflecting the effect of screening (sensitivity and specificity of testing for disease sub-states), the effectiveness of treatment by stage and disease-specific survival were those existing in the model except where stated with one exception. Model base parameters for sigmoidoscopy assume complete examination of the rectum, sigmoid colon and descending colon. The sensitivity estimates for the sigmoid and descending colon were reduced by factors reflecting reported rates of actual examination of those locations (17). Age and sex-specific rates of all-cause mortality for Canada were included to simulate ageing of the trial cohorts. OncoSim permits specification of participation rates in

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screening and reported trial-specific rates were used. Each trial cohort simulation was based upon 32 million simulated subjects.

**Review of RCTs**

A summary of the designs and study participants are contained in Table 1. Briefly, all studies randomized (using different schemes) subjects to be invited for sigmoidoscopy (with some also receiving fecal testing in NORCCAP). All studies included men and women aged 55-64 with 65-74 year olds also eligible for PLCO and 50-54 year olds also eligible for NORCCAP. Subjects with medical contraindications, CRC signs or symptoms or with a recent history of endoscopy were generally ineligible although study criteria were not identical. In three studies (UKFS, SCORE and NORCCAP) there was a single round of screening and in one (PLCO) there was a second round of sigmoidoscopy after 3-5 years. In NORCCAP some subjects assigned to the sigmoidoscopy arm additionally received fecal occult blood testing at the same time. Each study used specific management approaches for sigmoidoscopy-identified lesions in the rectum and distal colon, with some removing small isolated polyps at sigmoidoscopy without further intervention, and others sending all subjects with polyps to colonoscopy for subsequent management.

A summary of the subjects randomized and CRCs and CRC deaths in the cohorts is provided in Table 2. Average follow-up in the studies varied between 10.5-11.9 years. Each study observed reductions in the numbers of cancers and cancer deaths in the intervention compared to the control arms (19-22). Only the PLCO trial reported a significant reduction of proximal cancers

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(21) and no study reported significant reduction in the number of deaths attributed to proximal colon cancer.

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**Simulations**

OncoSim is a dynamic population model and immigration parameters for OncoSim-CRC were set to zero so that the cohorts were closed after initial entry. The Appendix provides a schematic for the model and provides the parameter values for sigmoidoscopy performance assumed in the simulations. Compliance rates with screening within the cohorts were as reported in the trials (Table 2).

Within OncoSim-CRC screening, sigmoidoscopy is not considered to be therapeutic and identification of polyps is assumed to result in referral to colonoscopy where lesions are managed; this is the protocol used in the PLCO trial. For NORCCAP, subjects found to have large polyps or small adenomas, are referred to colonoscopy. The effect of the NORCCAP management protocol on CRC can be simulated using the OncoSim-CRC sigmoidoscopy protocol. For the other two trials, small distal polyps identified by sigmoidoscopy were removed and only subjects at higher risk (based upon polyp size or the number or histology of removed smaller adenomas) were referred to colonoscopy. The effect of management strategies, where not all subjects with sigmoidoscopy detected proximal adenomas are referred to colonoscopy, were simulated within OncoSim-CRC by modelling that a screened subject received a simultaneous "screening colonoscopy and sigmoidoscopy" where the anatomic site specific sensitivities of the two tests were modified as follows. The screening colonoscopy had the sensitivity parameters for larger distal adenomas (6 or more mm for SCORE and 10mm or larger for UKFS), for proximal adenomas and for all cancers set to zero and sensitivity parameters for smaller distal adenomas remained at their base value. The simultaneous sigmoidoscopy had

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sensitivity parameters for smaller distal adenomas set to zero and used base values for all other states: subsequent diagnostic colonoscopy for an abnormal sigmoidoscopy used model base sensitivity for all disease states and anatomic sites. The joint effect of these modified screening colonoscopy and sigmoidoscopy interventions emulated the approach used in the UKFS and SCORE trials.

OncoSim-CRC allows screening tests to be simulated at regular intervals as specified during scenario creation. For UKFS, SCORE and NORCCAP only a single round of screening was used and no screening was reported outside of the study protocol, which can therefore be simulated without further modification.

In contrast to the other trials PLCO included two rounds of screening (baseline and at 3 or 5 years) and reported substantial endoscopy use outside of the trial protocol (21). Separate sets of simulations were performed to reflect second round screening performed at 3 years and at 5 years. Non-trial colonoscopy was reported at similar levels in the usual care and sigmoidoscopy arms after the trial screening period (i.e. > 5 years) (21) and we assumed that this occurred at equal rates in subjects screened or not screened in the first 5 years. Reported non-trial endoscopy screening in the trial screening period (0-5 years) was greater in the usual care arm than the sigmoidoscopy arm (21). We took reported rates of non-trial sigmoidoscopy and colonoscopy in each arm, adjusted for expected colonoscopy for follow-up of abnormal sigmoidoscopies, to estimate non-trial screening in the first 5 years. Independence was then assumed and screening patterns, both trial and non-trial, were determined. To estimate the

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potential effect of uncertainty in the distribution of non-trial endoscopy to subjects in each of the arms of PLCO two additional scenarios were modelled. For both scenarios, the reported rates of utilisation of non-trial endoscopy in the screening period (≤ 5 years) and post-screening period were maintained for both arms. The first scenario, 'Maxdiff', was one in which non-trial endoscopy use was assumed to occur in a way which maximized the difference between the two arms. This was achieved by allocating non-trial endoscopies to those not participating in trial screening in the intervention arm as much as possible and allocating non-trial endoscopy to the usual care arm so that the minimum number of individuals were screened. In the second scenario, 'Mindiff', the difference between the arms was minimized by reversing the above approach.

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## RESULTS

Table 3 provides a summary of the results of the results from the simulations and observed values from the trials. OncoSim predicted reductions in CRC incidence and mortality were within the 95% confidence intervals of the observed values for each of the trials.

Maxdiff estimates, those based upon allocating non-trial screens in the PLCO trial to maximize the predicted difference between the two arms, resulted in predicted increases in the reductions seen in the intervention arm from the original 22% to 31% for CRC incidence and from 27% to 35% for CRC mortality. Mindiff estimates were a 6% reduction for CRC incidence and 8% reduction for CRC mortality. The range of Mindiff to Maxdiff estimates were large and represent extreme cases and spanned the results seen in the PLCO trial (Table 3).

Observed differences in results from trials are influenced by multiple specific factors in addition to stochastic variability. In particular, participation in the baseline trial screening varies between 58% (SCORE) and 83% (PLCO) and compliance with a recommendation for diagnostic colonoscopy is also variable across the trials. This variability in compliance may obscure the influence of the effect of differing planned implementation of sigmoidoscopy screening between the trials. To remove the influence of variable participation we repeated the simulation of the trial results where compliance to both screening and follow-up was assumed to be 100%. Results of these calculations are provided in Table 4. As anticipated increased compliance resulted in increased incidence and mortality reductions associated with the intervention arm in

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each of the trials (Table 4). The UKFS and SCORE trials had the largest difference in predicted reduction in CRC incidence (26% v 18%) and CRC mortality (34% v 24%) at reported trial specific compliance levels (Table 4). At 100% compliance levels for both trials it was predicted that this difference would be removed and that SCORE would have slightly higher reductions than UKFS (Table 4). The predictions for UKFS and SCORE at 100% compliance (Table 4) can be compared to the per-protocol rates, which focus on screening participants, reported for these trials (19,20), which were respectively, 33% (95%CI=24%-40%) and 31% (95%CI=14%-44%) for CRC incidence, and 43% (95%CI=28%-55%) and 38% (95%CI=4%-60%) for CRC mortality. The predicted values from Table 4 for the two trials span the reported confidence intervals from the trials.

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## DISCUSSION

The study cohorts of the four trials were simulated within OncoSim-CRC which required multiple sets of simulations as the dynamic population based structure of OncoSim was different from the cohort structure of the clinical trials. We chose to compare the predicted and observed HRs and not the arm-specific incidence and mortality rates in each of the studies. We assumed, as is common, that HRs are transferable between populations and that any differences between arm-specific observed and model predicted rates may have reflected differences between Canadian population rates and those in the volunteer subjects in the trials from the different countries. The resulting predicted proportional reduction in CRC incidence and mortality rates in the intervention compared to control arms all lay within the confidence intervals of the same quantities observed in the trials. Uncertainty in the distribution of non-trial screens in the two arms of the PLCO lead to resulting uncertainty in predicted reductions and sensitivity analysis of potential distributions resulted in a range of estimates which spanned the observed values. The predicted effect of screening was increased when assuming 100% compliance and were compatible with per-protocol results reported for the UKFS and SCORE trials.

Numerous models have been published which simulate the effect of interventions, including screening, on the risk of developing or dying from colorectal cancer (23,24) and the value of this approach is well recognized (25,26). Models are calibrated, either formally or informally (27), against targets relevant to the context of their intended use. Nevertheless, calibration to common targets does not ensure that different models will provide similar predictions in identical

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scenarios (28). This has resulted in the recommendation that model expositions report predicted outcomes for standardized scenarios (29). A similar objective is met by fitting models to reports from published RCT's which also has the added benefit of providing an assessment against a validated standard (17).

In assessing CRC screening interventions it is common to use models projecting a lifetime cohort from the onset of planned screening until death (30). While such projections are recommended, especially for the economic analysis of potential screening options, observational data on important outcomes, such as disease and mortality risk, are only available for shorter timeframes. It is important to ensure that existing models provide satisfactory estimates of effects seen in the shorter time-frame of clinical studies, especially RCTs where available. While accord between screening RCT's and model prediction does not guarantee accuracy of longer term predictions it does provide some reassurance. This is true for OncoSim-CRC, where the results from the sigmoidoscopy RCTs are external, that is, they were not used in the original construction of the model and natural history parameters values were not adjusted to improve the fit between predicted and observed. Nevertheless, even with such validation it must be recognized that projections over many decades involve multiple uncertainties.

Models of cancer screening typically incorporate structures reflecting the underlying natural history of the disease, in this case CRC. In such models' predictions of screening effect rely upon the appropriateness of the assumed natural history process as much as on the modelled characteristics of the screening test. Natural history models are frequently complex and involve

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many parameters, some of which may be unobservable, whose values are estimated using diverse data and methods. In comparing observed and predicted outcomes of screening tests such as sigmoidoscopy, the underlying assumed natural history process is also being examined. Satisfactory agreement between predicted and observed outcomes for sigmoidoscopy screening would therefore increase the likelihood that other screening tests will have their effect accurately estimated if their specific test parameters are appropriately specified. Guidelines for cost-effectiveness analyses (31,32) emphasize the need for sensitivity analysis examining the impact of uncertainty in model parameter values on predicted outcomes. Predicting known outcomes from trials provides a valid method to assess the likely accuracy of predictions made by complex cancer models (16,17).

The PLCO trial was the most difficult to simulate as it had a second round of screening performed at variable times and substantial non-trial screening in both arms of the trial, both in the screening period and in the follow-up period (21). The published description of non-trial endoscopy in PLCO (21) was not sufficiently detailed to provide unique specification of the characteristics of subjects receiving these procedures for use in OncoSim simulations, so that some assumptions about their distribution were required, while maintaining the reported rates. We assumed that risk ratios, for both incidence and mortality, from the trials were transferable to the eligible Canadian population, but did not target that OncoSim reproduce the same rates of disease as reported in the trials. We reasoned that trial volunteers in Europe and the USA could have different CRC risks from the general Canadian population.

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## CONCLUSIONS

Four RCTs of sigmoidoscopy were modelled using the OncoSim-CRC platform which reproduced their results. Thus, it is likely that the underlying natural history model of OncoSim-CRC provides a reasonable representation of the disease process so that increased confidence can be placed in its use to inform the design of current, alternative and emerging colorectal cancer screening interventions as policy-makers increasingly weigh potential options.

**Declaration of Interest**: None

**Table 1:** Study Design of Sigmoidoscopy Trials

| | Study | | | |
|---|---|---|---|---|
| Trial Name | UKFS | SCORE | PLCO | NORCCAP |
| Country | UK | Italy | USA | Norway |
| Age eligible | 55-64 | 55-64 | 55-74 | 50-64** |
| Exclusion Criteria | History CRC, adenoma or IBD >1 fam hist. CRC, sig/colo < 3 years Symptoms CRC | History CRC, adenoma or IBD >1 1st deg fam hist. CRC, sig/colo ≤2 years Symptoms CRC | History CRC, * Endoscopy < 3 years | *Apply to screen group only:* Colorectal surgery, rad or chemo treatment, medical contras |
| Experimental Intervention | One time sigmoidoscopy | One time Colonoscopy reaching to sigmoid/descending junction | Baseline sigmoidoscopy and at 3-5 years | One time sigmoidoscopy or one time sigmoidoscopy + Qualitative FIT Colonoscope used |

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| | | | | |
|---|---|---|---|---|
| Control Intervention | None | None | None | None |
| Management | Remove all polyps <1cm at sigmoidoscopy | Remove polyps ≤5mm at sigmoidoscopy | Referral to family physician for further management | FS identified lesions >1mm were removed |
| Refer to Colonoscopy | Polyps ≥ 1cm or 3+ adenomas or tubulovillous/villous histology or dysplasia/CRC or 20+ hyperplastic polyps | Polyps ≥ 5mm or 3+ adenomas or tubulovillous/villous histology (>20%) or dysplasia/CRC | Guidance provided but at discretion of family physician | FS lesions >1cm or biopsied as adenoma or histology missing or subjects with +ve FIT were referred to colonoscopy |

*Other exclusion criteria related to other cancer endpoints

**Initial study included 55-64 only study was expanded in 2000 to recruit 50-54

**Table 2:** Accrual, Participation, Follow-up, Cancers and Cancer Deaths Hazard Ratios in the Trials

| | Study | | | |
|---|---|---|---|---|
| Trial name | UK Flex Sig | SCORE | PLCO | NORCCAP* |
| Country | UK | Italy | USA | Norway |
| Randomized to Sigmoidoscopy | M: 28,097<br>F:29,157 | M:8,576<br>F:8,572 | M:38,350<br>F:39,115 | M:9,900<br>F:10,103 |
| Sig Performed (Uptake rate) | M:20,519 (73%)<br>F: 20,155 (69%) | M: 5,269 (61%)<br>F: 4,642 (54%) | M:33,048† (86.2%)<br>F:31,610† (80.8%) | M: 6,299 (64%)<br>F: 6,661 (66%) |
| Eligible/Referred to Colonoscopy | 2,131 (2051- 96% received) | 832 (775-93.1% attended)<br>677 had complete study =80.4%) | 15,150† (11,241 – 74.2% attended) | 2,639 (2524 – 95.6% attended) |
| Average/Median follow-up time (years) | 11.2 | 10.5 (Inc)<br>11.4 (Mort) | 11.9 | 10.9 |
| HR of CRC Diagnosis | 0.77 (0.70-0.84)<br>Distal: | 0.82 (0.69-0.96)<br>Distal: | 0.79 (0.72-0.85)<br>Distal: | 0.80 (0.70-0.92)<br>Distal: |

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| | | | | |
|---|---|---|---|---|
| | 0.64‡ (0.57-0.72)<br>Proximal:<br>0.98‡ (0.85-1.12) | 0.76 (0.62-0.94)<br>Proximal:<br>0.91 (0.69-1.20) | 0.71 (0.64-0.80)<br>Proximal:<br>0.86 (0.76-0.97) | 0.76 (0.63-0.92)<br>Proximal:<br>0.90 (0.73-1.10) |
| HR of Death from CRC | 0.69 (0.59-0.82) | 0.78 (0.56-1.08)<br>Distal:<br>0.73 (0.47-1.12)<br>Proximal:<br>0.85 (0.52-1.39) | 0.74 (0.63-0.87)<br>Distal:<br>0.50 (0.38-0.64)<br>Proximal:<br>0.97 (0.77-1.22) | 0.73 (0.56-0.94)<br>Distal:<br>0.79 (0.55-1.11)<br>Proximal:<br>0.73 (0.49-1.09) |

*Results in this trial are for Sig and Sig+FIT combined.

†For first round

‡Screened versus control

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**Table 3**: Percentage Reduction in the Hazard Rates of CRC and CRC Death in the Four Trials and Estimated Reductions Using OncoSim-CRC

| | Reduction in Incidence (%) | | Reduction in Mortality (%) | |
|---|---|---|---|---|
| Trial | Observed (95%CI) | Predicted by OncoSim-CRC | Observed (95%CI) | Predicted by OncoSim-CRC |
| UKFS (19) | 23 (16,30) | 26 | 31 (18,41) | 34 |
| SCORE(20) | 18 ( 4,31) | 18 | 22 (-8,44) | 24 |
| NORCCAP(22) | 20 ( 8,30) | 26 | 27 (6,44) | 32 |
| PLCO (21) | 21 (15,28) | 22 | 26 (13,38) | 27 |

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**Table 4**: OncoSim-CRC Predicted Reduction in the Hazard Rates of CRC Incidence and CRC Death in the Four Trials Assuming Reported Rates and 100% Participation and Follow-up Compliance

| | OncoSim - CRC Predicted Reduction in Incidence (%) | | OncoSim - CRC Predicted Reduction in Mortality (%) | |
|---|---|---|---|---|
| Trial | Using Trial Reported Compliance Rates | Using 100% Compliance Rates | Using Trial Reported Compliance Rates | Using 100% Compliance Rates |
| UKFS | 26 | 36 | 34 | 47 |
| SCORE | 18 | 39 | 24 | 52 |
| NORCCAP –Sigmoidoscopy | 26 | 44 | 32 | 56 |
| NORCCAP –Sigmoidoscopy + Fecal Testing | 27 | 45 | 33 | 60 |
| PLCO | 22 | 47 | 27 | 54 |

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**APPENDIX**

**Appendix Table**: Screening parameters used in Simulations: Probability that an adenoma will be detected (sigmoidoscopy or colonoscopy) or that a test will be positive (Fecal Occult Blood) - %

| Procedure | Sigmoidoscopy | | Colonoscopy | | Fecal Occult Blood Test | |
|---|---|---|---|---|---|---|
| Region of Colon | Distal | Proximal | Distal | Proximal | Distal | Proximal |
| State | | | | | | |
| Adenoma 1-5mm | 75.0 | 0.0 | 75.0 | 65.0 | 4.0 | 4.0 |
| Adenoma 6-9mm | 85.0 | 0.0 | 85.0 | 85.0 | 10.0 | 10.0 |
| Adenoma ≥10mm | 95.0 | 0.0 | 95.0 | 87.5 | 30.0 | 30.0 |
| Cancer | 95.0 | 0.0 | 95.0 | 95.0 | 75.0 | 75.0 |
| Normal | 0.0 | 0.0 | 0.0 | 0.0 | 4.0 | 4.0 |

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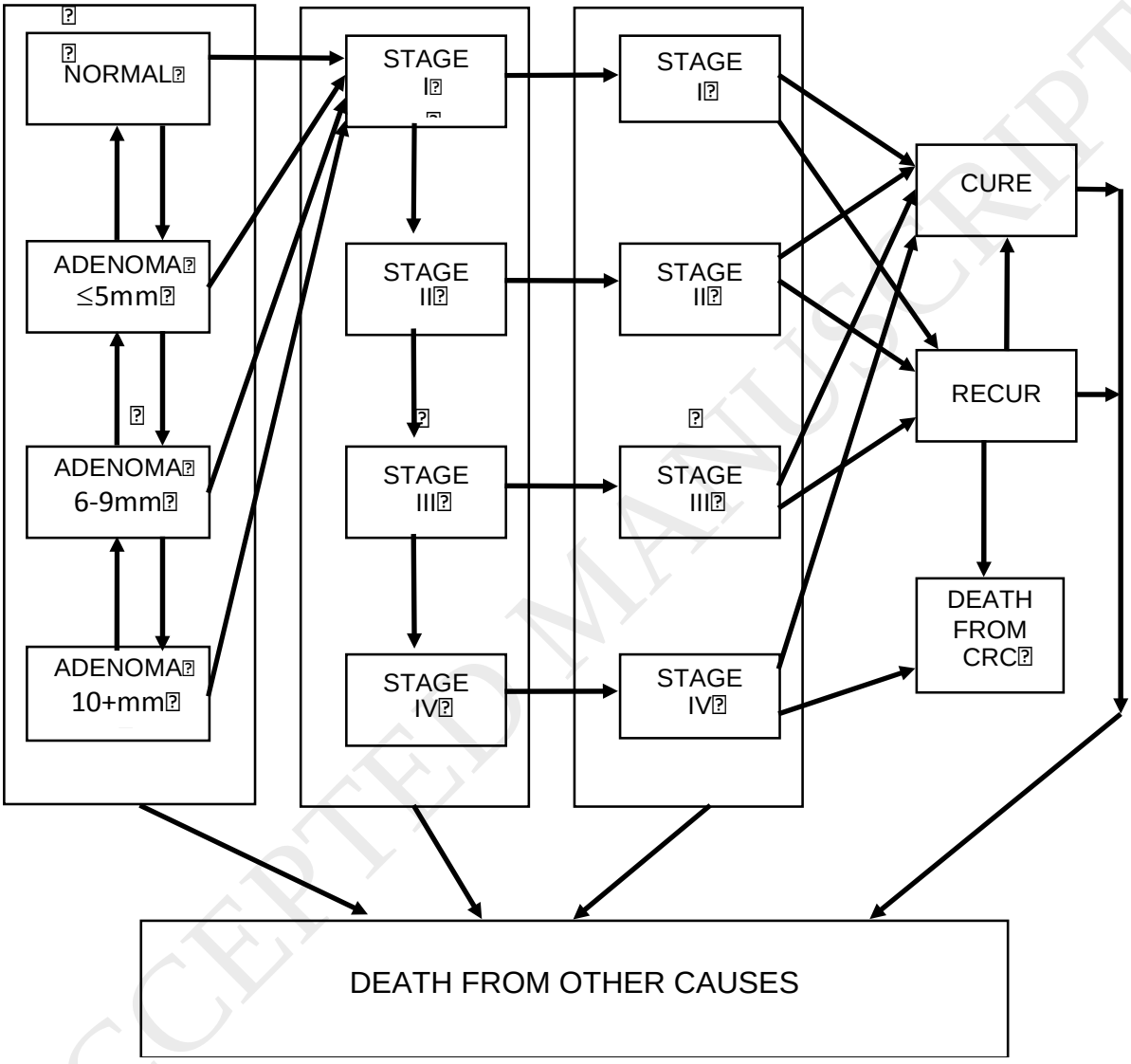
**Appendix Schematic:** CRC Development and Outcomes in the OncoSim CRC Model

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