

COLON CANCER CLINICAL TRIALS

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**In 2020, there
will be an
estimated
104,610 new
cases of colon
cancer and
43,340 cases of
rectal cancer
diagnosed in the
US (3rd highest).**



INTRODUCTION

WHAT ARE CLINICAL TRIALS?

National Institutes of Health Definition of a *Clinical Trial*

“A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.”

- Clinical trials are studies to **test new drugs, already approved drugs, devices, or other forms of treatments.**
- Many clinical trials look at **new ways to detect, diagnose, or measure the extent of disease.**
- Some even look at ways to **prevent diseases** from happening.
- Researchers still use **human volunteers**, who can leave at any time, to test these methods.

CLINICAL STUDY OR CLINICAL TRIAL?

Use the following four questions to determine the difference between a clinical study and a clinical trial:

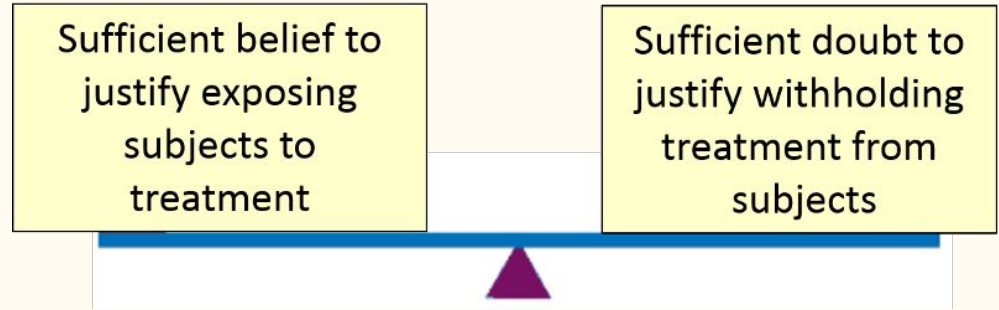


1. Does the study involve **human** participants? **Yes.**
2. Are the participants **prospectively** assigned to an **intervention**? **Yes.**
3. Is the study designed to evaluate the **effect** of the **intervention** on the participants? **Yes.**
4. Is the effect being evaluated a **health-related** biomedical or behavioral outcome? **Yes.**

WHY DO WE NEED CLINICAL TRIALS?

- It is ethical to conduct experimental studies only when there is a state of equipoise.

Equipoise is a “state of mind or belief characterized by a counterbalance of competing values, doubts, or risks”



- Clinical trials show us **what works** (and what doesn't) in medicine and health care.
- They are the best way to learn what works in **treating diseases** like cancer.
- Clinical trials are designed to **answer** some important **questions**.

Meinert, CL. Clinical Trials Dictionary: Terminology and Usage Recommendations. Baltimore, MD: The Johns Hopkins Center for Clinical Trials; 1996, p. 88.

Aschengrau, A., & Seage, G. R. (2020). *Essentials of epidemiology in public health*. Burlington, MA: Jones et Bartlett Learning, p. 206.

IMAGE: <https://sphweb.bumc.bu.edu/otlt/MPH-Modules/PH717-QuantCore/PH717-Module4-Cohort-RCT/PH717-Module4-Cohort-RCT11.html>

INCIDENCE RATE & MORTALITY RATE

Explore Cancers Further: Colon and Rectum Cancers

Cancer Incidence Rate, Race: All Races, 2012-2016

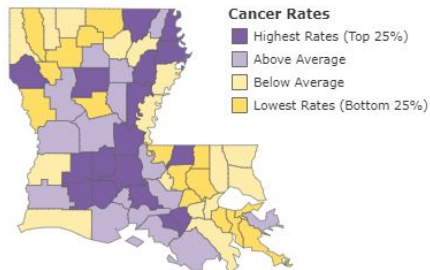
45.8 per 100k

Cases Diagnosed per 100k people (Incidence Rate)

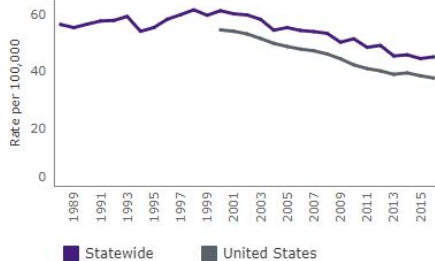
2,364

Cases Diagnosed per Year on Average

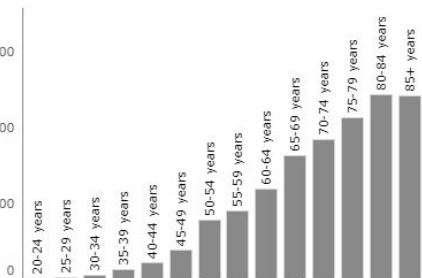
Differences by Geography



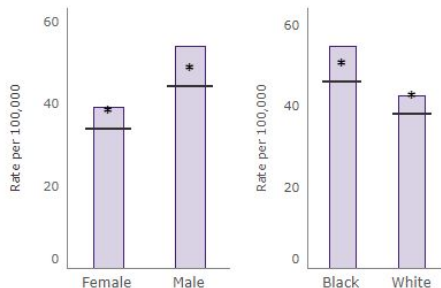
Changes over Time: 1988-2016



Differences by Age



Differences by Sex & Race



Notes:

Data represent the **average** rates and counts for the years 2011-2015 unless otherwise specified. An "*" on the bar charts indicates that Louisiana statewide rates are statistically significantly different from the U.S. average.

Louisiana Rates

U.S. Average

Explore Cancers Further: Colon and Rectum Cancers

Cancer Mortality Rate, Race: All Races, 2012-2016

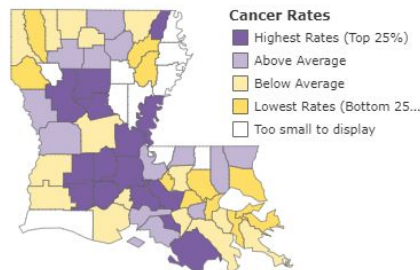
17.1 per 100k

Deaths per 100k people (Mortality Rate)

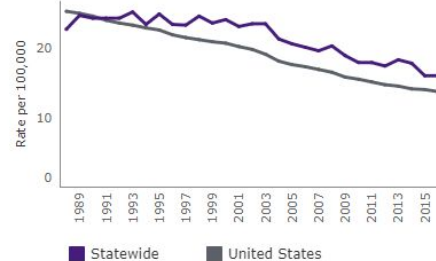
874

Deaths per Year on Average

Differences by Geography



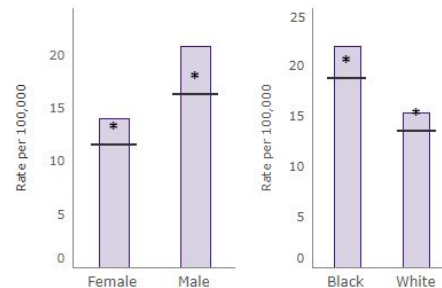
Changes over Time: 1988-2016



Differences by Age

Age distribution is not available for mortality data.

Differences by Sex & Race



Notes:

Data represent the **average** rates and counts for the years 2011-2015 unless otherwise specified. An "*" on the bar charts indicates that Louisiana statewide rates are statistically significantly different from the U.S. average.

Louisiana Rates

U.S. Average

TYPES AND PHASES OF CLINICAL TRIALS

A process that usually takes several years and is required for ALL new treatments...

- **Pre-clinical (or laboratory) studies**

- Clinical trials are done only after pre-clinical findings suggest that the new drug or treatment is likely to be safe and will work in people.
- Pre-clinical studies include cell studies and animal studies.

- **The investigational new drug (IND) application**

- **Phases of clinical trials...** Answer important questions such as:

- Phase 0 clinical trials: **Exploring if and how a new drug may work**
- Phase I clinical trials: **Is the treatment safe?**
- Phase II clinical trials: **Does the treatment work?**
- Phase III clinical trials: **Is it better than what's already available?**

- **Submission for FDA approval: New drug application (NDA)**

- Phase IV clinical trials: **What else do we need to know?**



PHASES OF A CLINICAL TRIAL



Preclinical LABORATORY STUDIES

Duration: Several years

- ✓ Provide information on dosing and toxicity levels



Phase 1 SAFETY

Duration: Several months

- ✓ Evaluate safety
- ✓ Gather information about how a drug interacts with the human body



Phase 2 SAFETY AND DOSING

Duration: Several months

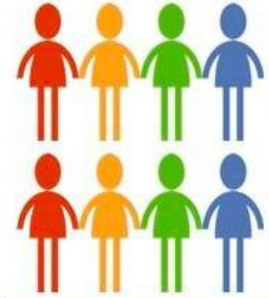
- ✓ Further evaluate safety
- ✓ Monitor side effects
- ✓ Check which dose works best
- ✓ Check effectiveness



Phase 3 SAFETY AND EFFICACY

Duration: Several years

- ✓ Confirm effectiveness
- ✓ Monitor safety



Phase 4 POST MARKETING SAFETY AND EFFICACY

- ✓ Gather information on the drug's effect in various populations and any side effects associated with long-term use

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COLON CANCER

DEFINITION:

- Cancer of the colon and/or rectum
- Often begins as a noncancerous polyp or adenoma growth

MECHANISMS:

Likely arises from one or a combination of:

- Chromosomal instability
- CpG island methylator phenotype
- Microsatellite instability

RISK FACTORS:

- Adenomatous polyps
- Age >50
- Inflammatory Bowel Disease (Polyps)
- History of Cancer
- Family History of Colorectal Cancer
- **Physical Inactivity/obesity**
- Smoking
- **Diets/Supplements**
- Race

DIAGNOSIS

SIGNS & SYMPTOMS:

- A persistent change in your bowel habits, including diarrhea or constipation or a change in the consistency of your stool
- Rectal **bleeding** or blood in your stool
- Persistent abdominal **discomfort**, such as cramps, gas or pain
- A feeling that your bowel doesn't empty completely
- Weakness or **fatigue**
- Unexplained **weight loss**

TREATMENT:

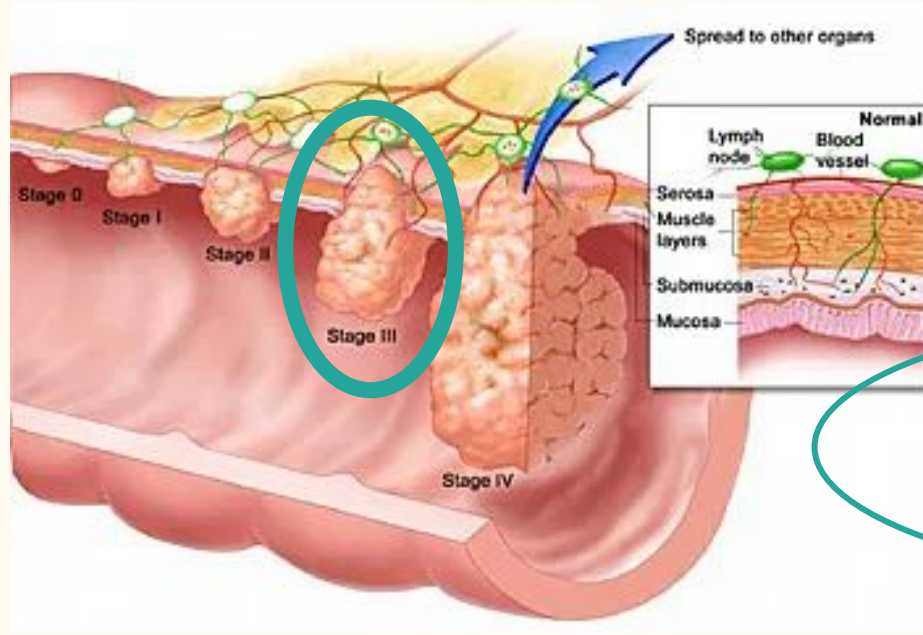
Local Treatments:

- Surgery
- Ablation/Embolization
- Radiation

Systemic Treatments:

- Chemotherapy
- Targeted Therapy
- Immunotherapy

COLORECTAL CANCER STAGES



STAGE I: IN SITU -- Cancers that have **not yet begun to invade** the wall of the colon or rectum

STAGE II: LOCAL -- Cancers that have **grown into the wall** of the colon or rectum, but have not extended through the wall into nearby tissues

STAGE III: REGIONAL -- Cancers that have spread through the wall of the colon or rectum and have **invaded nearby tissue**, or that have **spread to nearby lymph nodes**

STAGE IV: DISTANT -- Cancers that have **spread to other parts of the body**, such as the liver or lung



A doctor, wearing a white lab coat over teal scrubs and a stethoscope, holds a small wooden-framed chalkboard. The chalkboard has the words "CANCER PREVENTION" written on it in white chalk. The doctor's hands are visible holding the board, and the background is plain white.

CANCER
PREVENTION

2017	DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing	Physical activity ^{1,2}	Processed meat ³ Alcoholic drinks ⁴ Body fatness ⁵ Adult attained height ⁶
	Probable	Wholegrains Foods containing dietary fibre ⁷ Dairy products ⁸ Calcium supplements ⁹	Red meat ¹⁰
LIMITED EVIDENCE	Limited – suggestive	Foods containing vitamin C ¹¹ Fish Vitamin D ¹² Multivitamin supplements ¹³	Low intakes of non-starchy vegetables ¹⁴ Low intakes of fruits ¹⁴ Foods containing haem iron ¹⁵
	Limited – no conclusion	Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern	

PRIMARY PREVENTION:

1. Prevention of smoking and alcohol use
2. Prevention of weight gain
3. Maintenance of a reasonable level of physical activity in adulthood
4. **Limit red and processed meats**, high-fat dairy products, highly refined grains and starches, and sugars

POSSIBLE CHEMOPREVENTION:

1. Aspirin, NSAIDS
2. **Fiber**
3. **Physical Activity**
4. **Folic Acid**

Treatment Clinical Trials for Colon Cancer

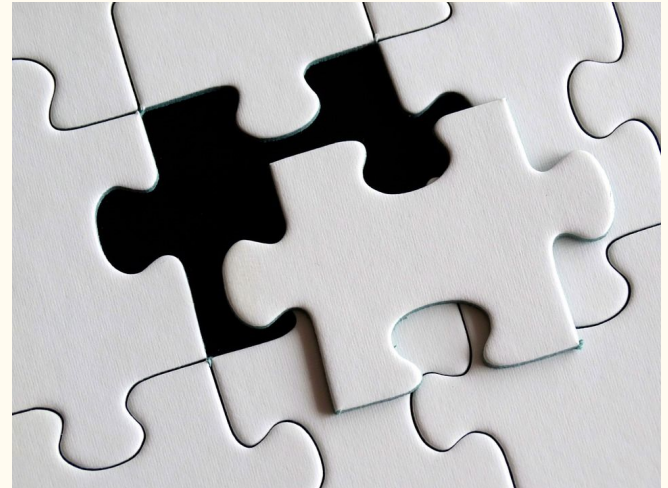
The National Cancer Institute (NCI) is currently supporting **47 treatment clinical trials for colon cancer**. Examples **relevant to this discussion** include:

- **TRIAL PHASE: NONE** -- The **Exercise** And Colon Cancer Treatment Trial
- **TRIAL PHASE: 0 (DRUG EFFECT)** -- Transcriptional Targets of **Vitamin D** in Patients with Stage I-III Colon Cancer or Resectable Colon Cancer Liver Metastases Receiving Preoperative Cholecalciferol
- **TRIAL PHASE: II (SAFETY & DOSING)** -- Marine **Omega 3** Fatty Acid in Treating Patients with Stage I-III Colon Cancer or Colorectal Mass or Polyp Undergoing Surgery
- **TRIAL PHASE: III (SAFETY & EFFICACY)** -- **Aspirin** for Dukes C and High Risk Dukes B Colorectal Cancers
- **TRIAL PHASE: III (SAFETY & EFFICACY)** -- **Vitamin D3** with Chemotherapy and Bevacizumab in Treating Patients with Advanced or Metastatic Colorectal Cancer, SOLARIS Trial

GAPS IN COLORECTAL CANCER RESEARCH

A 2018 study found **15 critical research gaps** in colorectal cancer (CRC):

- **RG2:** Insufficient evidence on precise contributions of genetic/environmental/**lifestyle factors** to CRC risk
- **RG3:** Pressing need for **prevention** trials
- **RG4:** Lack of **integration** of **different** prevention **approaches**
- **RG13:** Need to **increase** understanding of **health related quality of life** (HRQOL) and promote residual symptom resolution



RATIONALE

The function of the large intestine (colon and rectum) is to absorb water and electrolytes from food matter and eliminate feces.

- **FIBER:** Helps to maintain bowel health by absorbing water and adding bulk to stool. Often results in regulating bowel movements.
 - **Fiber may decrease risk of colon cancer by 27%.**
- **RED MEAT:** Often cooked at high temperatures that produce compounds (heterocyclic amines and polycyclic aromatic hydrocarbons) that can cause bowel cancer in people with a genetic predisposition.
 - **Red meat may increase risk of colon cancer by 28%.**
- **PHYSICAL ACTIVITY:** Exercise increases antioxidant levels and DNA repair. It can also affect growth factor production and insulin metabolism in ways that reduce inflammation and increase immune function.
 - **Physical activity may decrease risk of colon cancer by 24%.**

HYPOTHESIS: If these measures are *combined*, then colon cancer will decline further.

RESEARCH QUESTION

Will an integrated treatment approach involving increased fiber, decreased red meat, and increased physical activity cause a delay and/or reduction in the recurrence of colon cancer?



METHODS

RESEARCH STUDY DESCRIPTION

- **TITLE:** Preventing Colon Cancer Recurrence Through Diet and Exercise
- **GOAL:** This study will examine the biologic processes through which dietary interventions and physical activity **combined** may prevent disease recurrence in patients who have completed treatment for colon cancer.
- **OBJECTIVES:** To determine if a combination of moderate physical activity and improved diet can...
 - **PRIMARY:** Reduce systemic inflammation, quantified using plasma concentrations of high-sensitivity C-reactive protein, interleukin-6, and soluble tumor necrosis factor-alpha receptor two.
 - **SECONDARY:** Reduce (1) insulin resistance, (2) circulating tumor cells, and (3) tumor fraction.
 - **EXPLORATORY:** Improve (1) mitochondrial respiration rates and (2) fatty acid oxidation.

RANDOMIZATION & INTERVENTION

- **WAIT-LIST CONTROL: Usual Care (6 months) + Treatment Group 3 (6 months)**
 - INTERVENTION: Typical diet and physical activity (6 months) then treatment group 3 -- dietary intervention and physical activity (6 months)
- **TREATMENT GROUP 1: Dietary Intervention**
 - INTERVENTION: 6 Daily FiberCon Caplets (total of 12 g **fiber** daily) and no more than 113 g (4 oz.) of **red meat** twice per month
- **TREATMENT GROUP 2: Physical Activity**
 - INTERVENTION: weekly average of 10,000 **steps** (5 miles) per day
- **TREATMENT GROUP 3: Dietary Intervention and Physical Activity**
 - INTERVENTIONS: 6 Daily FiberCon Caplets (total of 12 g **fiber** daily), no more than 113 g (4 oz.) of **red meat** twice per month, weekly average of 10,000 **steps** (5 miles) per day

RESEARCH STUDY OVERVIEW

- **ALLOCATION:** Randomization
- **STUDY TYPE:** 3 part behavioral intervention model with parallel assignment
- **STUDY PHASE:** Not applicable
- **MASKING/BLINDING:** Double (Investigator, Outcomes Assessor)
- **DURATION:** One year (52 weeks)
- **PRIMARY PURPOSE:** Treatment
- **CONDITION UNDER STUDY:** Colon cancer
- **POPULATION:** Males and females 18 years of age or older with a previous diagnosis of colon cancer, a sedentary lifestyle, and not taking any dietary supplements
- **SAMPLE SIZE:** 200 (four groups of 50 randomized individuals each)
 - Determined based on estimated grant funds.

RESEARCH STUDY OVERVIEW

- **RISK:** Minimal & rare -- possible emotional distress, allergic reaction, infection or injury due to study procedures (No risk of death)
- **BENEFITS:** It is expected that the treatment will result in prevention or delay of colon cancer recurrence in at least 33% of the enrolled subjects.
- **RISK TO BENEFIT RATIO:** Potential benefits (preventing or delaying) colon cancer recurrence significantly outweigh the potential risks, which are not much greater than everyday life. Dietary change and exercise in isolation from one another have already been proven to be safe.
- **THERAPEUTIC ALTERNATIVES:** Existing polyp/cancer excision protocols, which are more invasive, if cancer redevelops
- **COST:** \$150,000-\$200,000 incentives & \$50,000 materials/procedures

RECRUITMENT: INCLUSION CRITERIA

- 
- Age ≥ 18 years
 - **Histologically-confirmed stage III colon cancer**
 - Completed surgical resection within 1-24 months
 - Completed chemotherapy (if applicable) within 1-24 months
 - Self-report, on average over the past one-month, less than or 90 minutes per week of moderate-intensity or vigorous-intensity physical activity
 - Provide written approval by physician or other qualified healthcare provider
 - No planned major surgery during the study period
 - Readiness to exercise [as determined by a modified version the **Physical Activity Readiness Questionnaire (PAR-Q)**]
 - Allow the collection and storage of specimens and data for future use
 - **Willing to be randomized**

RECRUITMENT: EXCLUSION CRITERIA

- **Evidence of metastatic colon cancer**
- **Concurrently actively treated other cancer**
- **Currently enrolled in another clinical trial of weight loss, physical activity, or dietary intervention**
- **Current body mass greater than or equal to 181 kg**
- **Former weight loss surgery**
- **History of regularly taking fiber supplements**
- **Unable to provide a baseline fasting blood sample**
- **Unable or unwilling to give informed consent**
- **Unable or unwilling to be randomized**
- **Or any other condition that may impede testing of the study hypothesis or make it unsafe to engage in the exercise program**



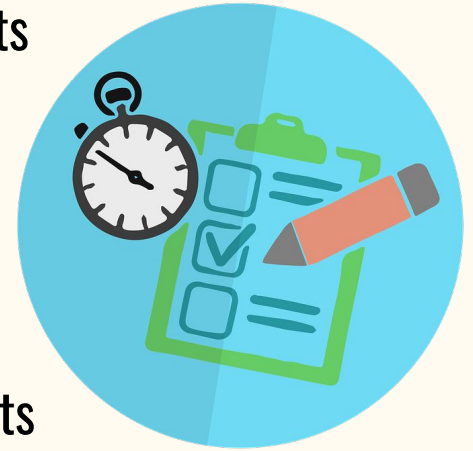
DESIGN

NUMBER OF VISITS: 6

- Screening: 1
- Baseline Visit: 1
- Follow-up Visits: 4 (1 every 3 months for 1 year)
- *NOTE: Participants earn \$50 at each visit + Potential \$20 per month bonuses (for time and travel)*

VISIT PROCEDURES: (NO COST TO PARTICIPANTS)

1. Vital signs (blood pressure, pulse, etc.)
2. Medical history and physical exam
3. Body measurements (height, weight, etc.)
4. Questionnaires (PAR-Q, etc.)
5. Oral glucose tolerance tests
6. ECG
7. DXA
8. Blood tests
9. Urine tests
10. Fitness assessment
11. Replenish fiber supplements



MONITORING & INCENTIVES

- **MONITORING:**

- **DIETARY GROUP: Amazon Fire HD 8 Plus**
(with daily alarm reminder set)
- **PHYSICAL ACTIVITY GROUP: Fitbit Versa 3**
with Heart Rate Tracking



- **INCENTIVES:**

- **Prevent/delay colon cancer recurrence**
- **Keep technology** provided
- **\$50** at each 3 month clinic visit **(for time and travel)**
- **\$20 bonus** per month of 75% or greater treatment methodology compliance
 - *NOTE: Dietary intervention group will earn bonus based on rate of daily entering of diet checklist NOT on compliance to diet. They will not be incentivised to potentially lie. Only incentivised to report daily.*

RESULTS

DATA

STORAGE:

- Will utilize **Genius eDocumentum** -- a digital archiving solution that meets regulatory requirements for the Trial Master File (TMF)
- Stored for **6 years** after completion of research
- Accessible for inspection and copying by authorized representatives

CONFIDENTIALITY:

- **DATA SHARING:** Blinded data will be shared with the **investigator** and the **outcomes assessor**.
- **RECRUITMENT:** Upon completion of the study, **participant contact information** (for those that opted in) will also be shared with clinical trial participant **recruiters** within the organization in order to potentially enroll them in other studies they may be interested in.

MULTIVARIATE REGRESSION ANALYSIS



Will be performed to look for potential **confounders** such as:

- Age
- Sex
- Race/ethnicity
- Education
- Socioeconomic status
- **Alcohol consumption**
- **Tobacco consumption**
- Initial BMI
- Environmental exposures

OTHER CONSIDERATIONS

POTENTIAL BARRIER: 6 required visits will occur during regular workday/week

BIAS:

- **Selection bias minimized** due to randomization and investigator blindedness but possible due to **differential losses to follow-up**.
- Potential for **information bias** when participants enter daily dietary intake vs. steps that are automatically recorded.
- **Interviewer and misclassification bias** minimal/unlikely (PAR-Q only).

PERFORM:

- **Intent-to-treat analysis** at at beginning after randomization to preserve the benefits of randomization.
- **Stratified analyses** according to age, race, family history, etc.
- **Effect Measure Modification**

CALCULATE in SAS:

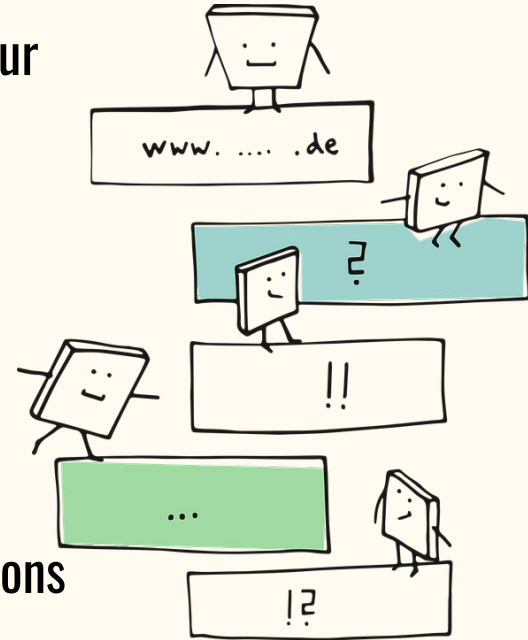
- Chi-squared
- T-test
- Linear Regression
- Relative risk ratio

DISCUSSION

GAPS IN COLORECTAL CANCER RESEARCH

A 2018 Research Study Found 15 Critical Research Gaps in Colorectal Cancer (CRC):
(Lawler et al., 2018)

- ***RG1:*** Lack of realistic models that recapitulate tumour/tumour micro/macroenvironment
- ***RG2:*** Insufficient evidence on precise contributions of genetic/environmental/lifestyle factors to CRC risk
- ***RG3:*** Pressing need for prevention trials
- ***RG4:*** Lack of integration of different prevention approaches
- ***RG5:*** Lack of optimal strategies for CRC screening
- ***RG6:*** Lack of effective triage systems for invasive investigations
- ***RG7:*** Imprecise pathological assessment of CRC



Lawler, M., Alsina, D., Adams, R. A., Anderson, A. S., Brown, G., Fearnhead, N. S., ... & Koelzer, V. H. (2018).

Critical research gaps and recommendations to inform research prioritisation for more effective prevention and improved outcomes in colorectal cancer. *Gut*, 67(1), 179-193.

GAPS IN COLORECTAL CANCER RESEARCH

- **RG8:** Lack of qualified personnel in genomics, data sciences and digital pathology
- **RG9:** Inadequate assessment/communication of risk, benefit and uncertainty of treatment choices
- **RG10:** Need for novel technologies/interventions to improve curative outcomes
- **RG11:** Lack of approaches that recognise molecular interplay between metastasising tumours and their microenvironment
- **RG12:** Lack of reliable biomarkers to guide stage IV treatment
- **RG13:** Need to increase understanding of health related quality of life (HRQOL) and promote residual symptom resolution
- **RG14:** Lack of coordination of CRC research/funding
- **RG15:** Lack of effective communication between relevant stakeholders

Lawler, M., Alsina, D., Adams, R. A., Anderson, A. S., Brown, G., Fearnhead, N. S., ... & Koelzer, V. H. (2018).

Critical research gaps and recommendations to inform research prioritisation for more effective prevention and improved outcomes in colorectal cancer. *Gut*, 67(1), 179-193.

LIMITATIONS & CONSIDERATIONS

- Colon cancer **preventative research** studies with combined intervention methodologies have been **minimal**.
- These types of studies are **dependent on grants** because a pharmaceutical company is not potentially going to recoup the cost by getting a new drug or device onto the market.
- The proposed study was of a relatively short duration (1 year) and had a sample size of only 200 participants.
- **FUTURE: Longitudinal studies** (spanning a couple of decades) that include **thousands** of individuals with a **family history** but no recorded incidence of colon cancer that also incorporate **multiple preventative** interventions would be ideal.

CONCLUSION

Due to the high incidence of and unpleasant treatment options for colon cancer, more effective and **coordinated preventative treatment** protocols could potentially save **save countless numbers of lives** and **improve the quality of life** of many more.

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