

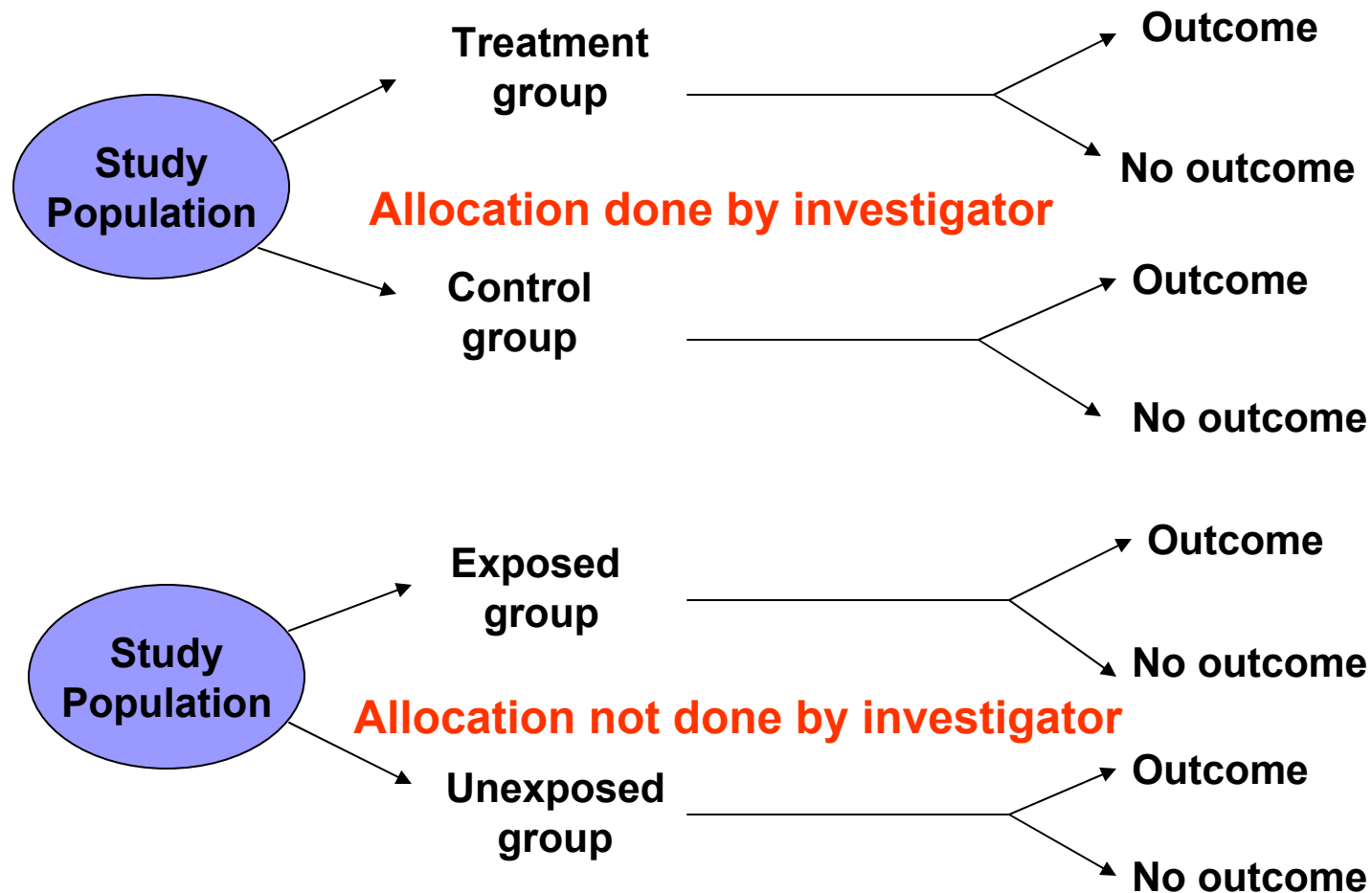


Moving From Observational Studies to Clinical Trials: Why Do We Sometimes Get It Wrong?

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Clinical Trial vs. Cohort Study





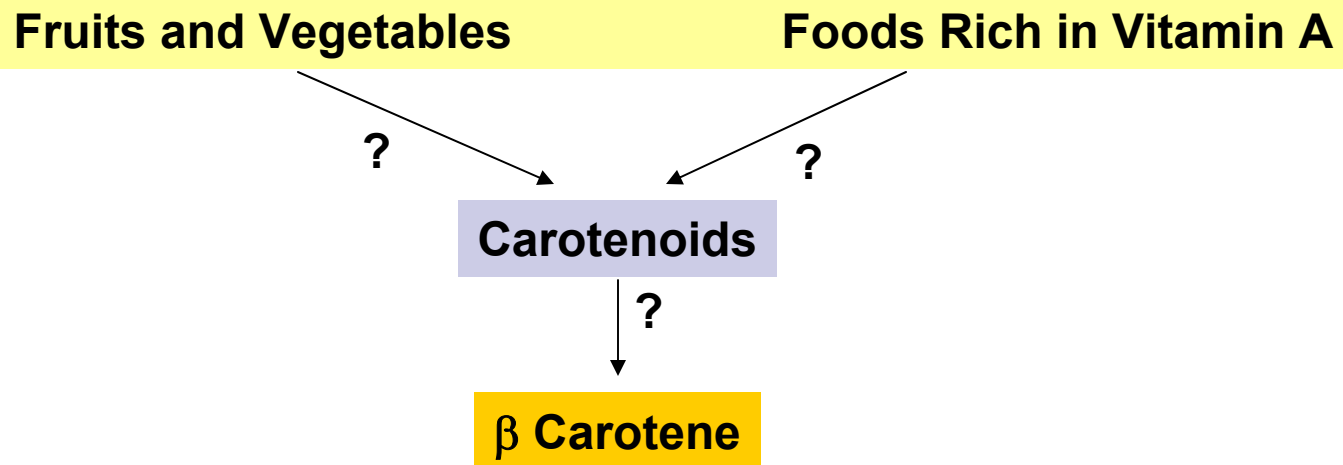
β Carotene and Lung Cancer




β Carotene and Lung Cancer: What Did We Know Prior to RCTs?

- β carotene is found in high concentrations in carrots and dark green leafy vegetables.
- β carotene is postulated to have anticancer effects—among the most efficient quenchers of singlet oxygen molecules.
- Observational epidemiologic studies: Individuals who consume high amounts of foods rich in β carotene or whose blood levels are high experience approx. 20-40% lower risk of developing cancer, including lung cancer.
- Because confounding could be likely in observational studies, RCTs are needed to determine whether β carotene prevents cancer.
- Dosage for optimal benefit was speculative.

β Carotene and Lung Cancer: What Did We Know Prior to RCTs?





β -Carotene: An Unusual Type of Lipid Antioxidant

At higher oxygen levels, β carotene loses its antioxidant activity and shows an autocatalytic, pro-oxidant effect, particularly at relatively high concentrations. Similar oxygen-pressure-dependent behavior may be shown by other compounds containing many conjugated double bonds.

Burton GW and Ingold KU. Science 224:569-573, 1984

Characteristics of RCTs of β Carotene

Study	PHS	ATBC	CARET	Linxian
β -carotene dose (add'l agents)	50 mg qod (aspirin)	20 mg (α -tocoph)	30 mg (Vit A)	15 mg (Se, α -tocoph)
Follow-up (yrs)	12	6	4	5
% ever smokers	50	100	98	30
Plasma β -carotene post-intervention (ng/ml)	1200	3000	2100	860
RR lung cancer	0.95 (incid) 1.02 (mort)	1.18 (incid) 1.08 (mort)	1.28 (incid) 1.17 (mort)	0.87 (mort, all cancers)




Secondary Analysis of β carotene Trials of Lung Cancer

- **CARET**
 - RR = 0.80 for former smokers
 - RR = 1.42 for current smokers
- **ATBC**
 - RR = 0.97 for 5-19 cigarettes/day
 - RR = 1.25 for 20-29 cigarettes/day
 - RR = 1.28 for more >29 cigarettes/day
- **PHS**
 - RR = 0.78 for nonsmokers
 - RR = 1.00 for former smokers
 - RR = 0.90 for current smokers




β Carotene and Lung Cancer: What Do We Know Now?

- No overall benefit of β carotene for smokers.
- Wide array of molecular responses identified that may account for adverse events in smokers.
- β carotene is not a very potent antioxidant and has various other actions.
- No anti-cancer effects of β carotene for well-nourished populations.
- Plausible that any chemopreventive action of β carotene supplementation is confined to poorly nourished individuals (Linxian).
- Individuals who eat high quantities of fruits and vegetables have lower risk of death from various chronic diseases.




“Nutritional epidemiology is qualitatively incapable of identifying a dietary compound(s) that will be efficacious”

F. Meyskens



“As if we were searching for a new therapeutic compound, we have expected high doses of a single nutrient to reproduce the beneficial effects of the complex nutrient mixtures found in whole foods. Perhaps this basic assumption is wrong.”

T. Byers, CA Cancer J Clin, 1999



“The clinical trials ought to be seen as representing a triumph of the scientific process rather than a failure of therapy. We now know that β carotene supplements are not an effective means of lowering the risk of cancer... No one should discount the importance of epidemiologic studies of diet and chronic diseases. Persons who eat a relatively large quantity of vegetables, fruits, and grains have a profoundly lower risk of death, particularly from cardiovascular disease and cancer.”

ER Greenberg, MB Sporn, NEJM 1996



Studies of Adenoma Recurrence

RCTs of Adenoma Recurrence

Study	Intervention	Yrs f/u	RR
McKeown-Eyssen	Cereal fiber 20g	2	1.2
MacLennan	Cereal fiber 25g β -carotene 20mg	4	1.2 1.5
Greenberg	β -carotene 25mg Vit E 400 IU+ Vit C 1g	4	1.01 1.08
Baron	Calcium 1.2 g	4	0.83*
Alberts	Cereal fiber 13g	3	0.99
Schatzkin	F&V, \uparrow fiber, \downarrow fat	4	1.00
Baron	Aspirin 81mg Aspirin 325mg	4	0.81* 0.96
Alberts	UDCA	3	0.89

*statistically significant



Strengths and Limitations of Adenoma Recurrence Studies: Is it the Right Model?

STRENGTHS

- Prospective nature
- Investigation of etiology of adenoma formation
- Detection bias minimized
- Relatively short-follow-up period needed for end point analysis

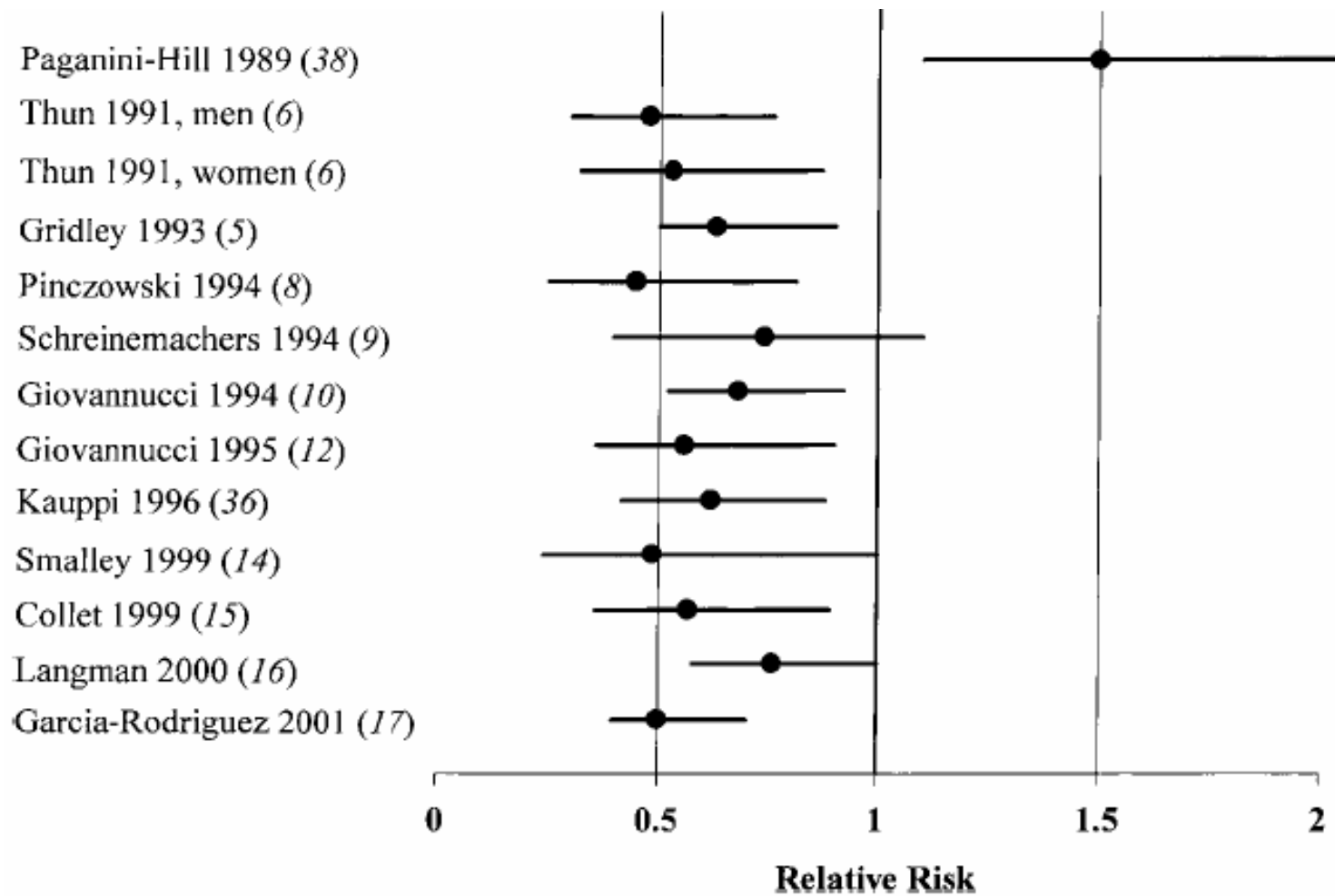
LIMITATIONS

- Selectivity of population and limited generalizability
- Assessment of premalignant lesion rather than invasive cancer
- Investigating risk factors related to early events in carcinogenesis pathway
- Short duration in follow-up from exposure to end point



NSAIDs and Colorectal Neoplasia

Cohort Studies of NSAIDs and Colorectal Cancer



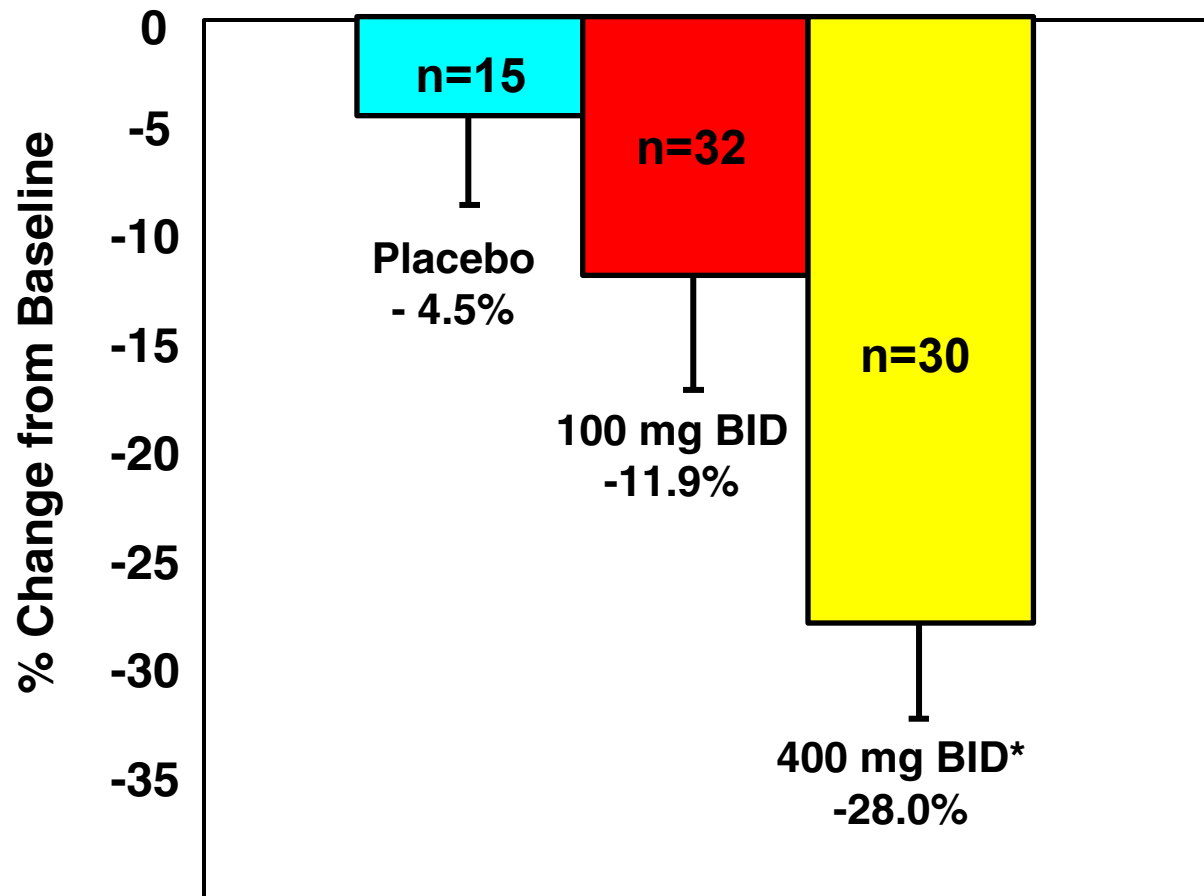
Thun, et al., JNCI, 2002



Colorectal Cancer and Adenomas Have High Incidence of COX-2

- 85% of cases positive at both the RNA and protein levels
- 40-50% of colorectal adenomas showed significant elevation of COX-2

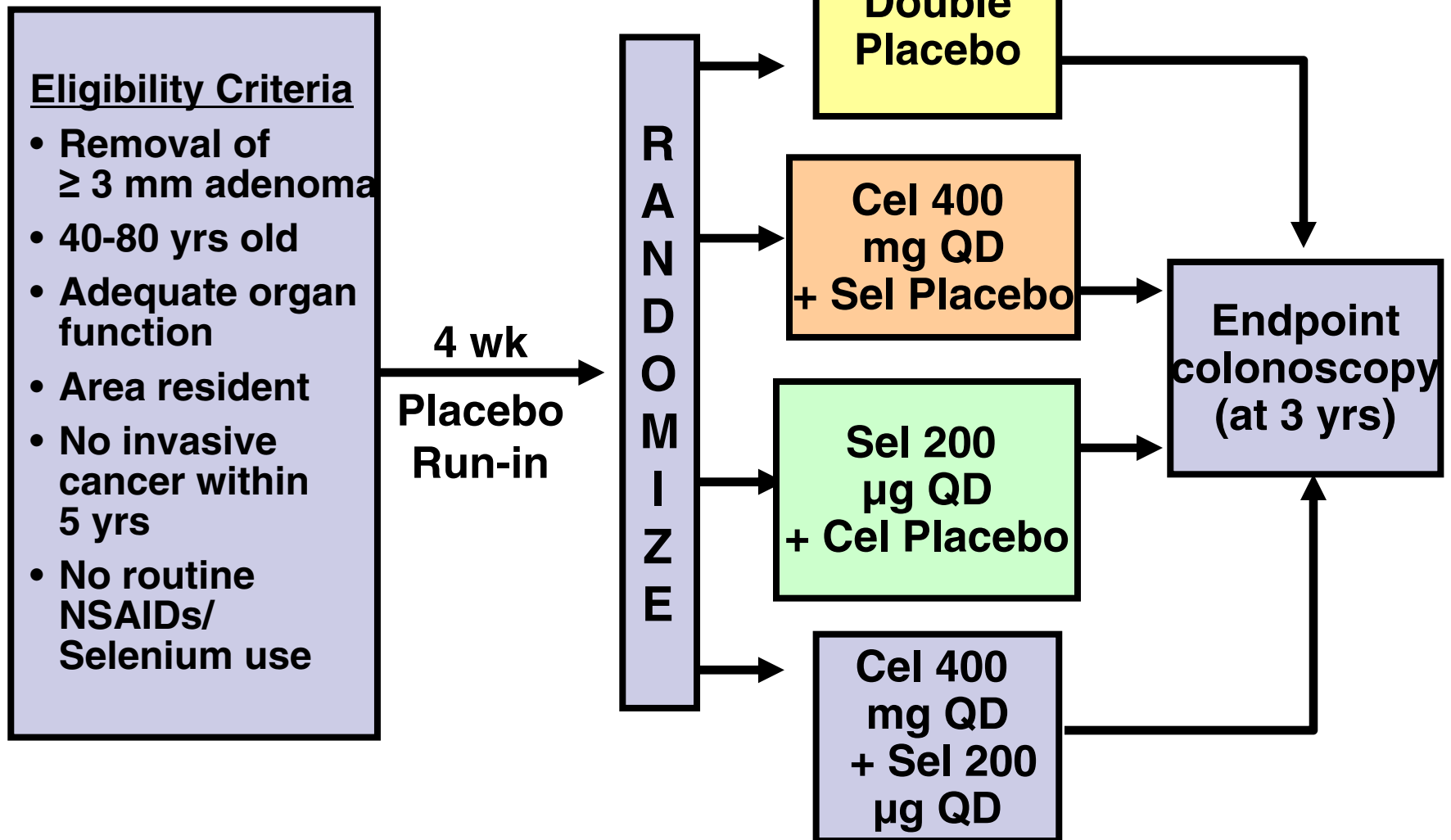
Effect of Celecoxib in Familial Adenomatous Polyposis: Percent Change in Number of Polyps After Six Months of Treatment



* p = 0.003 versus placebo

Steinbach et al., NEJM, 2000

Celecoxib/Selenium Trial Schema (Pre-December 20, 2004)



FDA Statement

FOR IMMEDIATE RELEASE
Statement
December 17, 2004

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

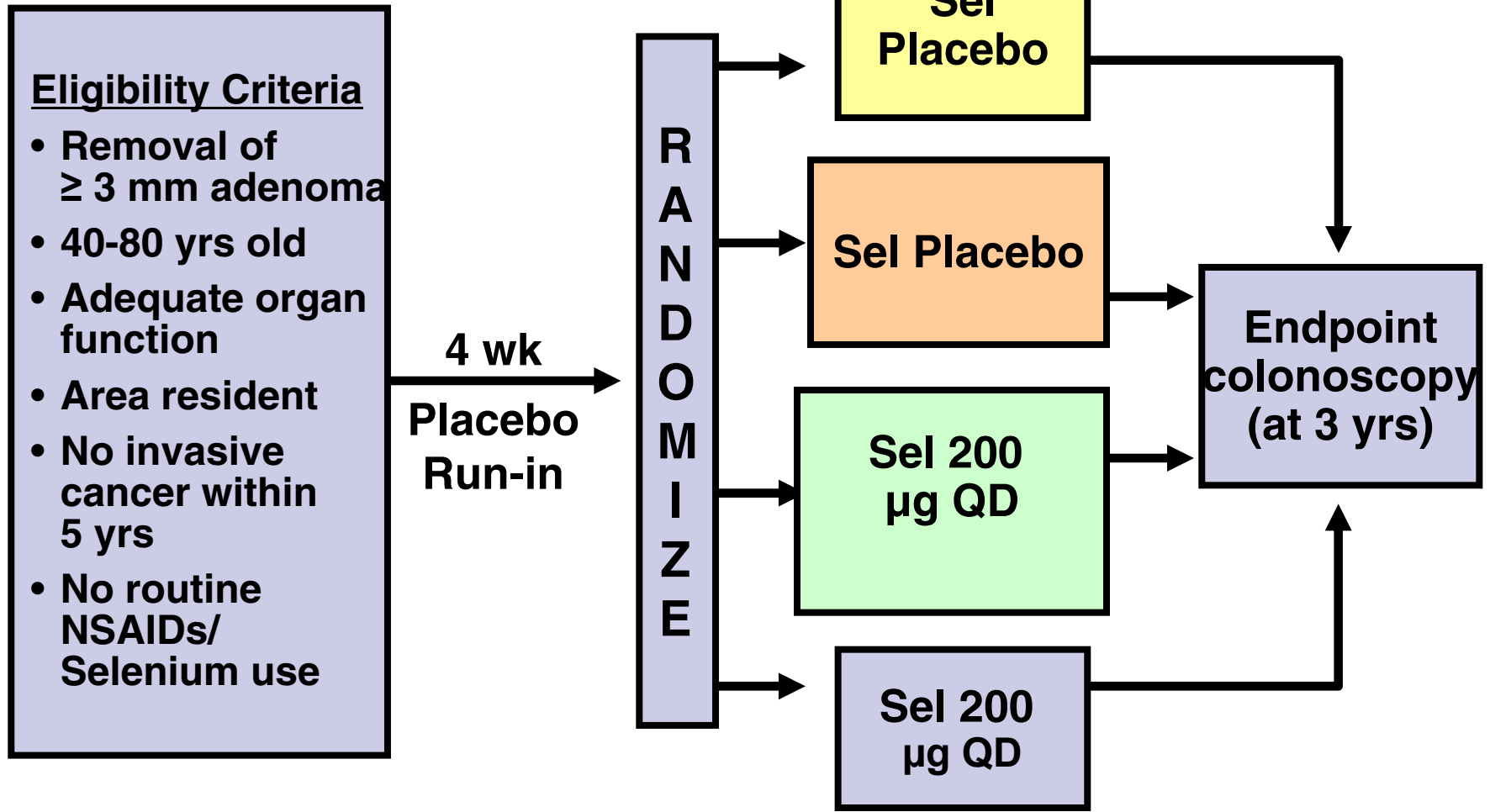
FDA Statement on the Halting of a Clinical Trial of the Cox-2 Inhibitor Celebrex

The FDA today released the following statement on the halting of a clinical trial of the Cox-2 inhibitor Celebrex (celecoxib):

The Food and Drug Administration (FDA) learned last night from the National Cancer Institute (NCI) and Pfizer, Inc., that NCI has stopped drug administration in an ongoing clinical trial investigating a new use of Celebrex (celecoxib) to prevent colon polyps because of an increased risk of cardiovascular (CV) events in patients taking Celebrex versus those taking a placebo.

Patients in the clinical trial taking 400 mg. of Celebrex twice daily had a 3.4 times greater risk of CV events compared to placebo. For patients in the trial taking 200 mg. of Celebrex twice daily, the risk was 2.5 times greater. The average duration of treatment in the trial was 33 months.

Celecoxib/Selenium Trial Schema (Post-December 20, 2004)



A Question of Balance: Chemoprevention Trials Require Both a High Level of Efficacy and Safety





Safety of Chemoprevention Trials

- What evidence on toxicity of the agent should preclude the launching of a RCT?
 - Previous trials might not have considered this adequately
 - Phase II trial data on toxicity needed
 - How much toxicity are we willing to tolerate? None? Minimal?

Themis and Justice



Removing the blindfold...Moving Forward





Moving Forward...

- Systematic development of chemopreventive agents is a long process, multi-factorial process
- All available evidence must be considered and any missing pieces must be disclosed or filled in
- Development of studies that will identify safe and efficacious agents that can be integrated into routine preventive medical practice
- As a research community, we need guidelines to inform that process in the most useful way
- Models have been proposed (i.e., Meysken's algorithm). Such models will need to be validated using existing RCTs
- Next generation of RCTs will need to incorporate lessons learned so far



Lessons Learned

- Must test effects of nutritional supplements given in broader combinations, and in more modest doses, thereby simulating the micronutrient combinations in the matrix of whole foods
- We should critically appraise observational methodology as well as limitations of RCT design
- Trials should be designed to be long-term, testing nutrients over many years among people at average risk
- Must acknowledge agent's anti-carcinogenic potential as well as disruption of normal homeostasis



Future Directions

- Do we continue searching for the “magic bullet”?
- Should we consider a pill as an alternative to lifestyle practices (i.e., diet, exercise, tobacco)?
- Do we continue to believe that a RCT is necessary before fully accepting a factor as protective? Some lifestyle factors are not amenable to double-blind RCTs.
- All agents must be suspected of adverse effects; don't just focus on their potential benefits.