Yakult

Science for Health

1495 UNIVERSITY OF ABERDEEN

The Rowett Institute

HUMAN STUDIES

SERIES TWO: FUNDAMENTALS OF RESEARCH

Created in partnership with
The Rowett Institute, University of Aberdeen

Similarities and Differences between Medical and Food Studies in Humans

Strict ethical rules exist for both types of studies, guiding researchers running any type of human study. These may differ from country to country, although the underlying principles are the same:

Participants must be protected from potential harm and must not be asked to do anything that is unnecessary and does not add value to the study.

Type of product for each study:

Food (includes probiotics and prebiotics) – has a nutritional or health promoting value upon consumption. These are not designed to prevent, treat or cure disease, but may help alleviate symptoms or maintain health.

Food supplements – includes probiotics and prebiotics in capsules, tablet, powder or liquid. In Europe these studies will be judged by European Food Safety Authority (EFSA).

Medical products – when there is a therapeutic end-point to treat or prevent disease, live microorganisms are considered drugs, and will be judged by the European Medicines Agency (EMA). This category may include Live Biotherapeutic Products, (LBPs), which can also be based on probiotics.

COMPARISONS BETWEEN A MEDICAL STUDY VS. FOOD STUDY

Process	Medical study	Food study
Ethical approval	CTIMP (Clinical Trial of an Investigative Medical Product)	Local ethical approval committee (usually)
Medical professional on study team	Yes	No (but in some studies a qualified healthcare professional may be required e.g. trained phlebotomist for blood sample collection)
Invasive tissue samples can be collected	Yes (Example - biopsies)	No (usually limited to saliva, blood and faecal/urine samples). May be by nasal/ oral/faecal swabs.
Study must be registered prior to start, with clearly defined outcomes	Yes (FDA/EMA requirement)	Yes (FDA/EFSA requirement)
Adverse outcomes must be reported	Yes	Yes
Product under investigation must be regarded as 'safe for consumption' or have a history of safe use	No (but needs to be established in a Phase I study)	Yes

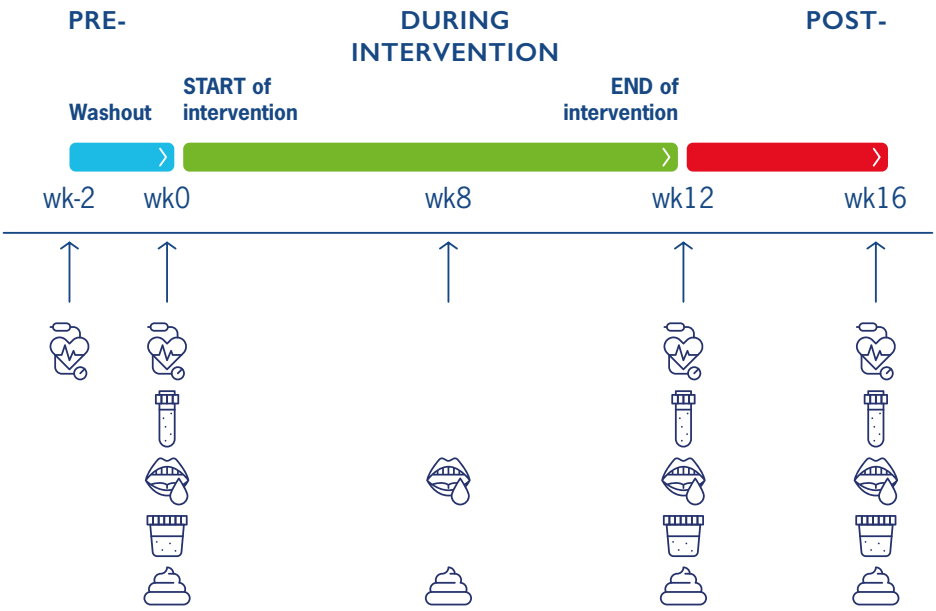
FDA: Food and Drug Administration (U.S.A.)
EFSA: European Food Safety Authority

Sample	Types of analysis
Saliva	Microbiota, cortisol, Immunoglobulin A (sIgA), etc.
Blood	Blood cells, immune markers, glucose, insulin, hormones, vitamins, etc.
Urine	Microbiota, metabolites
Faeces	Microbiota, metabolites (including short-chain fatty acids, SCFA), calprotectin, etc.

NOTE: Different samples require different collection, transport, storage and extraction methods.

The preservation of stool samples, for example, requires preservation in adapted buffer solutions and temperature control, in order to preserve the integrity of the microbial DNA and RNA. Maintaining viability of aerobic and anaerobic bacteria in the sample might also be crucial for later isolation and quantification.

PROBIOTIC RESEARCH: EXAMPLE OF STUDY DESIGN AND SAMPLE COLLECTION



SAMPLE COLLECTION

Blood pressure – measure during visit but more accurate to have 24hr continuous monitoring

Saliva and breath samples - measures oral microbiota and fermentation gases (H_2 / CH_4)

Faecal samples - for intestinal microbial profiling (composition and function)

Blood samples - fasted samples for glucose tolerance and insulin sensitivity (and others as required)

Urine samples - measures circulating metabolites of intestinal origin - includes products released from microbial activity (24hr collection or spot overnight sample)

Additional samples - Ileostomic samples from ileostomy bags in colonic surgery patients. Biopsy samples can also be taken but are very hard to obtain from healthy individuals (samples mucosal rather than luminal content)

The ideal scenario is that participants attend study centre in person and provide fresh samples in a controlled environment for all measures - but with higher participant burden.

NOTE: Balance what is *acceptable* for participants with what is *essential* for the study.

Faecal samples should be stored frozen at -70°C in a cryoprotectant buffer or processed quickly (within 12hr of defecation).

Different transport buffers may be required depending on analysis - specific collection kits can be used for posting samples to the study centre to avoid the need for in-person visits.

QUALITY CHECKS

Questions to think about in assessing study quality

WAS THE STUDY APPROPRIATELY REGISTERED?

IS THE STUDY DESIGN CLEAR AND APPROPRIATE? (E.G. IS THERE A DIAGRAM?)

IS THE TYPE OF STUDY (**PARALLEL OR CROSSOVER***) AND THE NUMBER OF PARTICIPANTS JUSTIFIED?

*See more information on the following page

ARE THE SAMPLE COLLECTION, STORAGE, PROCESSING AND ANALYSIS METHODS CLEARLY EXPLAINED AND VALIDATED?

ARE THE SAMPLES TO BE COLLECTED APPROPRIATE FOR THE ANALYSIS METHODS?

ARE THE EXPECTED OUTCOMES CLEARLY EXPLAINED AND ACHIEVABLE?

HAVE APPROPRIATE PARTICIPANTS BEEN RECRUITED, AND PROPERLY RANDOMISED TO DIFFERENT STUDY ARMS?

HAVE THE NUMBERS OF PARTICIPANTS COMPLETING THE STUDY BEEN REACHED (AND ANY REASONS FOR DROPPING OUT GIVEN)?

HAVE POTENTIAL ADVERSE EVENTS BEEN PROPERLY DESCRIBED AND REPORTED?

More info on study design quality:
www.theanalysisfactor.com/study-designs-health-research-evidence-hierarchy/

IS THE FINAL STATISTICAL ANALYSIS PROPERLY PRESENTED AND EXPLAINED?

HAS COMPLIANCE OF PARTICIPANTS BEEN MONITORED AND REPORTED?

QUESTIONS TO THINK ABOUT IN ASSESSING STUDY QUALITY

Randomised, controlled, double-blind, parallel study (scenario 1)

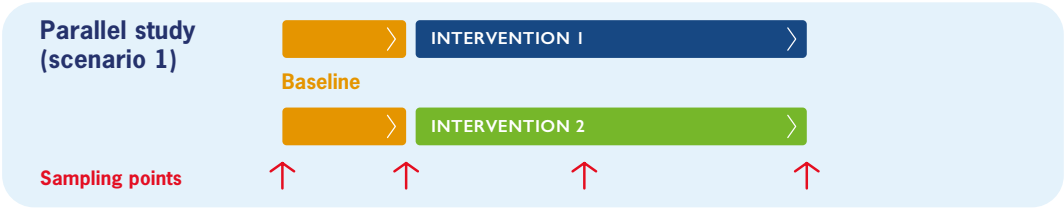
- Randomised means that participants are allocated to the placebo or intervention arm of the study, in a randomised way
- Controlled means that the treatment group is compared to a non-treated group. The latter can be "treated" with a placebo, or can be a defined group that is monitored in the same way, but not treated. In the case of a placebo we talk about a *randomised, double-blind, placebo-controlled study.*
- Double-blind means that neither the participant nor the researcher knows which treatment is received. This means that both the placebo and intervention product have to look identical. The "code" is only broken at the end of the study.
- Parallel means that both arms occur simultaneously

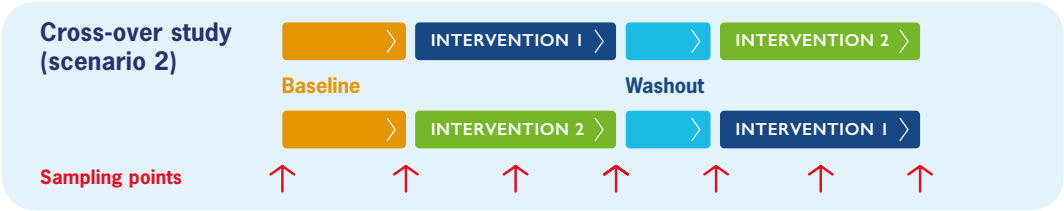
Randomised, controlled, double-blind, cross-over study (scenario 2)

- The cross-over aspect additionally means that all participants receive both supplements (Placebo and treatment), in either order.
- This has the advantage that each participant can act as their own control, making any findings more robust, and requires a smaller study population.
- The disadvantages are that studies take longer and may span different seasons and holidays that may have an effect. Additionally, effects in the first phase may persist, meaning that the starting point for the second phase is different.

Further Learnings

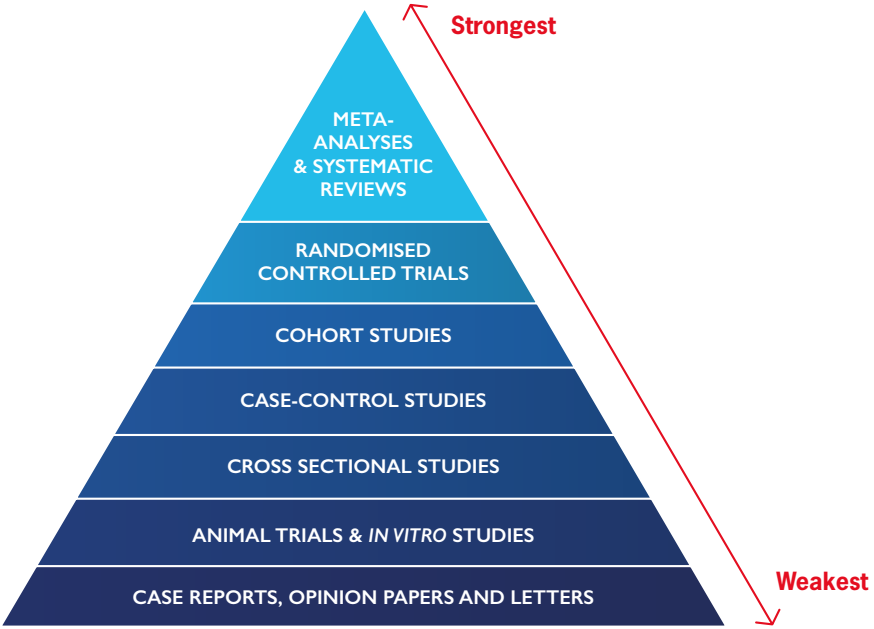
- A well-designed study with fewer participants can provide as robust information as a poorly designed one with 100s of participants.
- Generally cross-over studies need fewer participants to generate meaningful data.
- It may be useful to split the final statistical analysis into responders and non-responders; this needs to be announced at the start of the study though.





See the study design quality pyramid on the following page

HIERARCHY OF EVIDENCE



Study design can be thought of as a pyramid:

- High-quality studies with the 'best evidence' are positioned at the top. There are generally fewer of them.
- Weaker-evidence studies are positioned at the bottom. These are generally cheaper, easier and therefore more commonly found.
- Different study designs with varying levels of evidence will fit into this pyramid hierarchy.

Ultimately, the study design has to be appropriate for the question(s) being asked in the study.