Think Beyond.

LESSONS LEARNED

from **25** years and **11** studies on

Inflammatory Bowel Diseases

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INFLAMMATORY BOWEL DISEASES

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Epidemiology

Cases per 100,000 person per year

Ulcerative Colitis: 6.3-24.3
Crohn's Disease: 5-20.2
Lymphocytic Colitis: 1.1-5.2
Collagenous Colitis: 3.1-5.5

- With lower incidence and prevalence rates in Asia and the Middle East

Probable **sustained increase** of incidence and prevalence especially in **Western countries**

Risk factors

(especially in Western countries)

Smoking

Infections, gut dysbiosis and antibiotics

Diet ("Western diet") and dietary / nutrient intolerances

Unusual sleep duration

Psychosocial factors

Low physical activity & obesity

NSARs

MILESTONE LEARNINGS

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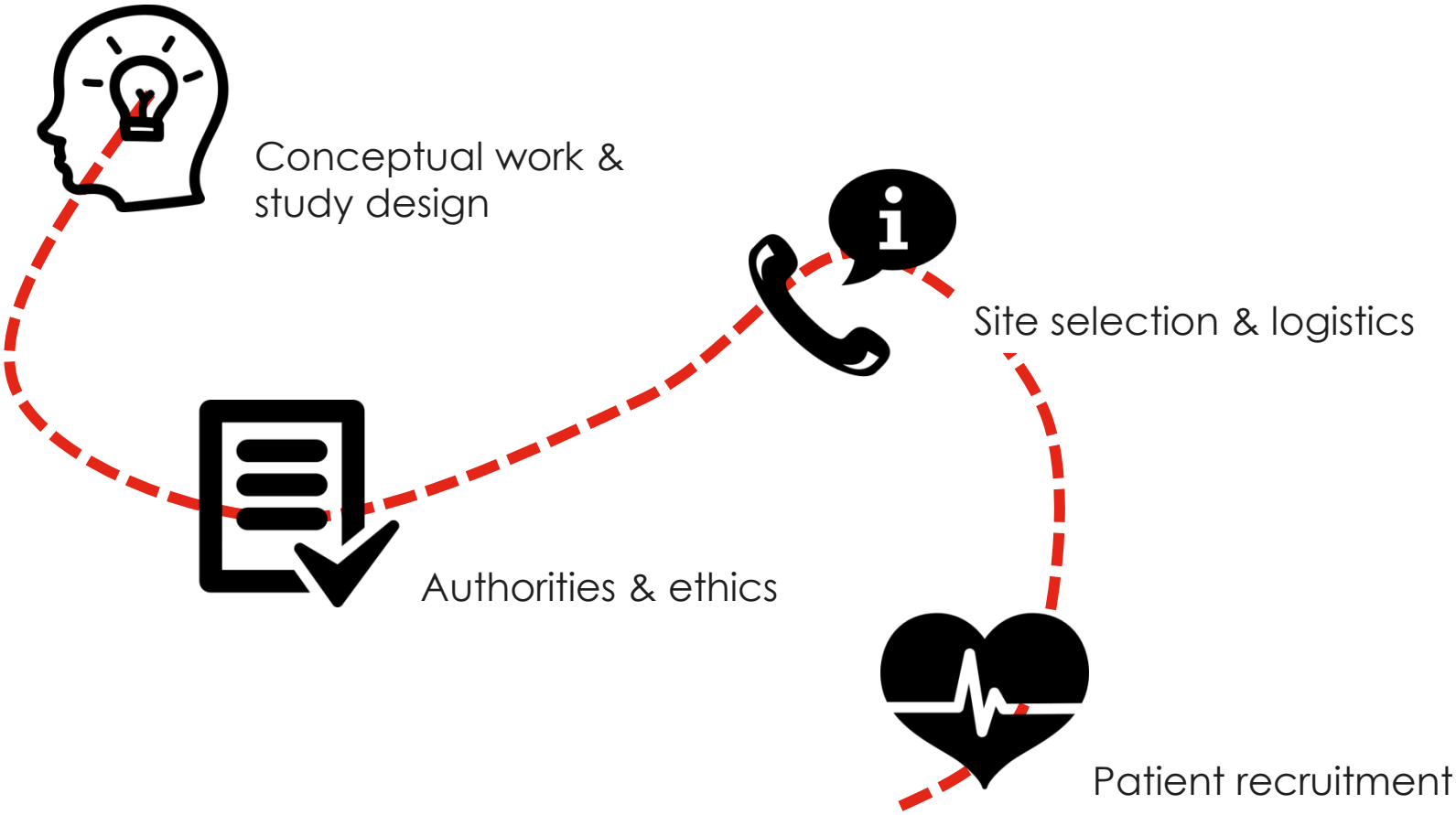
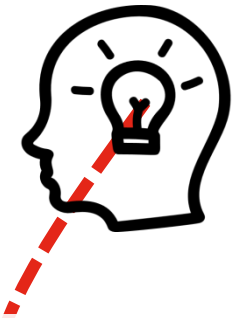


CONCEPTUAL WORK & STUDY DESIGN



LEARNINGS
Conceptual work & study design

- Carefully select **efficacy endpoints.**
  The following efficacy scores are commonly used:
  - Clinical Activity Index (CAI)
  - Modified Disease Activity Index (mDAI)
  - Endoscopic Index (EI)
  - Histological Index (HI)
  - Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

- Keep in mind that the **efficacy scores** have different scales, however, in some domains may overlap. Thus, some scores/**sub-scores** might "contradict" each other.

- Diary based scores require an **intensive training** for all involved site personnel and monitors, as well as for patients. Patients need to understand the **importance of the diary** and to keep it up to date. This effort might be undermined if too many scores (diaries) are imposed on the patients.

- Keep **patients informed** in order to achieve high motivation for diary completion. In young patients, **digital diaries** on handheld devices or web based may increase cooperation.

AUTHORITIES & ETHICS

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- Consider the **disease stage** and choose objectives and endpoints accordingly (e.g. induction of remission vs. prevention of relapse).

- Primary endpoints should reflect the **disease activity**. Note that the validity of common disease activity indices is not always certain. Thus, choose indices that include **signs and symptoms**.
  CAVE: endoscopy is not compulsory as a primary endpoint as it may be confounded with time lag and observer variation.

- Clinical **severity** and anatomic extent should be accounted for (e.g. by stratification).

- Treatment **response** should be only a secondary endpoint.

LEARNINGS
Authorities & ethics

- Plan sufficient **wash-out periods**, especially for corticosteroids.

- Based on objectives, **study duration** needs to be adjusted
  - induction of remission at least 8-12 weeks
  - maintenance (prevention of relapse) at least 12 months and at least 12 week FU

- Select an **active comparator**; keep in mind that topical corticosteroids are regarded as having also systemic effects by some authorities and ECs. Therefore consider immunological **inclusion / exclusion** criteria (e.g. immunization).

SITE SELECTION & LOGISTICS

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- Ensure that sufficient patient **numbers** can be provided by the sites; consider that an increased study complexity may lead to high **screening failure** rates.

- Consider **regulations** on tissue sample shipment and conditions for lab samples.

Conceptual work
Study design

LEARNINGS
Site selection & logistics

- Endoscopy follow-ups should be performed by the same investigator to avoid **inter-rater variances** in severity rating.

Authorities & Ethics

- If histological examination is planned, consider a **central pathologist** in order to avoid inter-rater / regional variances in histological scores.

- Avoid **diagnostic errors,** by ensuring that the endoscopy is performed by an investigator having experience in detecting even rare IBDs.

Patient recruitment

PATIENT RECRUITMENT

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- Epidemiological studies indicate **2 age peaks** (15-40 and 50-80 years). However, it remains unclear if etiology is the same in both age groups. Therefore consider **age stratification** in the analysis strategy.

- **Racial and ethnic** differences have been described, as well as **geographic** (north/south gradient) and **socio-economic** (e.g. risk) factors that affect IBD prevalence and severity.

- Be aware of slight **female predominance** in the patient population, especially women in late adolescence and early adulthood. Consider gender stratification in analysis strategy as well as appropriate **contraceptive** measures, taking into account that hormonal contraception might alter disease activity.

- Consider stratifications according to **smoking** status, co-morbidities and **co-medication.**

- Consider **dietary** factors and/or restrictions – e.g. exclude predictable dietary modifications.

LEARNINGS
Patient recruitment

Choose Passion!

Think Beyond.

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