A Phase III double-blind placebo-controlled Randomised Trial of Aspirin on Recurrence and Survival in Colon Cancer Patients

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FAGG approval: 11 July 2017
Ethical Committee approval: 31 July 2017

PROTOCOL SIGNATURE SHEET

A Phase III double-blind placebo-controlled Randomised Trial of Aspirin on Recurrence and Survival in Colon Cancer Patients

ASPIRIN trial

BE **2017-001397-41**

Version: v5.0- Belgium (26 March 2020)

I have read this protocol and agree that it contains all necessary details for carrying out this study. I agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki.

Name + function	Site	Signature	Date

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1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ADL	Activities of Daily Life Questionnaire
AE	Adverse Event
AFAP	Attenuated Familial Adenomatous Polyposis
APC	Adenomatous Polyposis Coli
ASA	American Society of Anesthesiologists
BCC	Basal-cell carcinoma
CAP	Capecitabine (Xeloda) OX- oxaliplatin (Eloxatin)
CAPOX	Chemotherapy regimen consisting of capecitabine combined with oxaliplatin
CBPL	Commissie voor de Bescherming van de Persoonlijke Levenssfeer (Privacy Commission)
CEA	Carcinoembryonic antigen, tumour marker
CIN	Cervical intraepithelial neoplasia
CRC	Colorectal Cancer
CSCs	Colon cancer stem cells
CTCAE	Common Terminology Criteria for Adverse Events
CXCL1	Chemokine Ligand 1
DOAC	Direct Oral AntiCoagulants
DFS	Disease Free Survival
DSCA	Dutch Surgical Colorectal Audit
DSMB EORTC	Data Safety Monitoring Board European Organisation for Research and Treatment of Cancer
(e)CRF	(electronic) Case Report Form
EudraCT	European drug regulatory affairs Clinical Trials
FAGG	Federaal agentschap voor geneesmiddelen en gezondheidsproducten
FAP	Familial Adenomatous Polyposis
FOLFOX	A chemotherapy regimen for treatment of colorectal cancer, made up of the drugs folinic acid-fluorouracil-oxaliplatin

GCP	Good Clinical Practice
GI	Gastro-Intestinal
GMP	Good Manufacturing Practice
HLA	Human leukocyte antigen
IADL	Instrumental Activities of Daily Living
IB	Investigator's Brochure
IC	Informed Consent
IFN	Interferon
iFOBT	Immunochemical fecal occult blood test
IL	Interleukin
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LMWH	Low molecular weight heparin
LUMC	Leiden University Medical Center
MAP	MYH-Associated Polyposis
MIC	Macrophage Inhibitory Cytokin
NFU	Netherlands Federation of University Medical Centres; in Dutch: Nederlandse Federatie van Universitair Medische Centra
NSAID	Nonsteroidal anti-inflammatory drug
OS	Overall Survival
PIK3CA	Phosphatidylinositol 3-kinase catalytic 110-KD alpha
Po	Per os
PPI	Proton-pump inhibitor, medication for reduction of gastric acid production
PROs	Patient Reported Outcomes
PTGS	Prostaglandin-G Synthase
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma

SPC	Summary of Product Characteristics
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TNM	Tumour Node Metastasis
TTF	Time to Treatment Failure
UICC	Union for International Cancer Control
UZA	Antwerp University Hospital (Dutch: Universitair Ziekenhuis Antwerpen)
QLQ	Quality-of-Life Questionnaire

2. SUMMARY

Rationale: Preclinical, epidemiologic and clinical evidence suggest that acetylsalicylic acid use may reduce overall cancer risk and mortality in colon cancer patients.

Objective: To investigate acetylsalicylic acid 80 mg po daily for 5 years as an adjuvant therapy in curatively operated, stage II and III colon cancer patients.

Study design: A phase III double-blind placebo-controlled randomised trial of adjuvant low- dose acetylsalicylic acid in colon cancer patients. The question will be addressed by means of two parallel studies in patients treated with or without adjuvant chemotherapy.

Study population:

- Patients 45 years and older with histologically confirmed adenocarcinoma of the colon
- Patients must have TNM stage that is one of the following: pT3-4; N0-2 and M0, or pT1-2 and N1-2 (Union for International Cancer Control (UICC) stage II and III) (in case of >1 tumour: more advanced tumour is stage II or III)
- Patients must have completed surgical resection (R0) (both laparoscopic and open surgery) within 12 weeks of randomisation

Exclusion:

- Patients with rectal cancer (defined as tumour within 15 cm from the anal verge)
- Patients currently taking oral anti-coagulants or use of low molecular weight heparin (LMWH) or use of DOACs
- Patients currently taking (low-dose) acetylsalicylic acid or other anti-aggregantia for any reason
- Patients with a history of bleeding disorders or active gastric or duodenal ulcers
- Patients currently taking high dose systemic glucocorticoids (≥ 30 mg predniso(lo)n or equivalent)
- Patients with (suspected) (non-) polyposis syndrome (Familial Adenomatous Polyposis (FAP)/ Attenuated Familial Adenomatous Polyposis (AFAP), MYH-Associated Polyposis (MAP), Lynch syndrome)
- Patients with >100 polyps of the colon **or** a known hereditary syndrome of the colon in a first degree family member
- Allergy or intolerance to salicylates
- Patients with local or distant recurrent disease
- Previous malignancies other than cervical intraepithelial neoplasia (CIN) or squamous cell carcinoma (SCC) with a disease free survival *less than* 5 years
- Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Intervention: Patients will be randomised for acetylsalicylic acid 80 mg po daily for 5 years versus placebo.

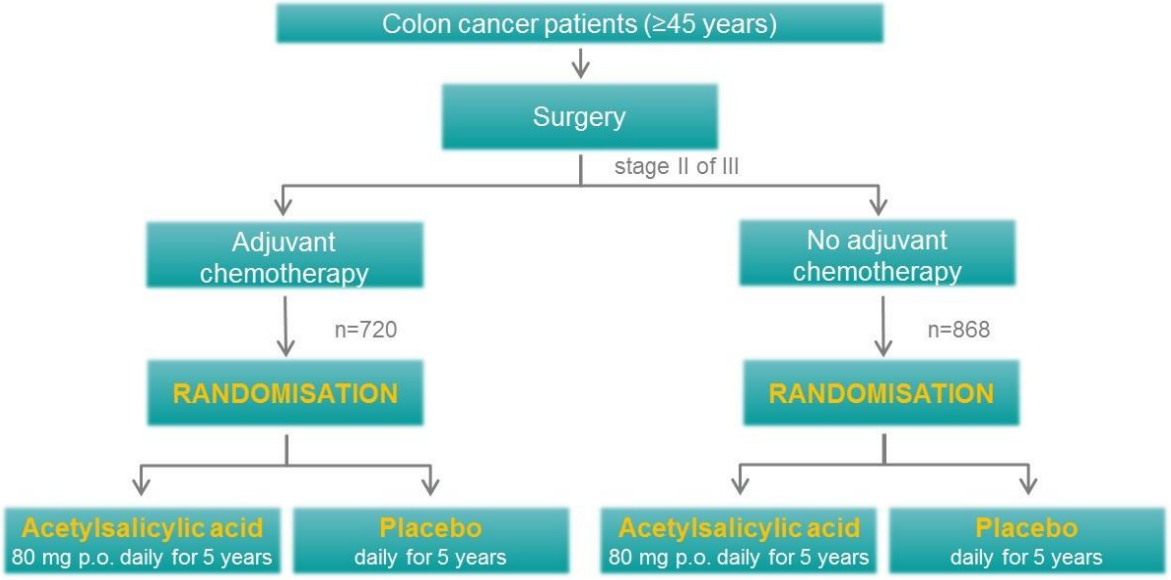
Main study parameters/endpoints: The primary endpoint of the trial is 5year Overall Survival (5-yr OS). Secondary endpoints are Time to Treatment Failure (TTF; time elapsed between randomisation until treatment discontinuation due to disease recurrence, unacceptable toxicity, death or any other event of interest) and 3-year Disease Free Survival (DFS); time to recurrence or death due to any cause. The trial is powered to identify a hazard ratio of 0.75 in the acetylsalicylic acid arm, with 80 percent power and a type 1 error of 0.05 (2-sided). In order for the trial to be successful, 1588 patients need to be randomised.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Unexpected adverse events may occur. Given the widespread use of low-dose acetylsalicylic acid in cardiovascular risk management, it is unlikely that new toxicities will be identified. However, adverse anti-cancer effects may be identified. An independent data safety monitoring board will oversee trial conduct. A planned interim futility analysis allows early termination of the study if it appears that acetylsalicylic acid will not favourably impact colon cancer outcome.

International Collaboration

This trial is part of a collaboration with the Dutch ASPIRIN trial (NL 38132.058.14). The rationale for this collaboration is to accelerate accrual. Both protocols are similar in such a way that allows data to be pooled for analysis. One database will be used to collect all data for both countries, central data management will be performed by the Datacenter Department of Surgery of the Leiden University Medical Center (LUMC) in Leiden, The Netherlands. The total number of required patients will be 1588 of which 400 patients will be randomised in the Belgium trial.

3. FLOW CHART ASPIRIN TRIAL



Primary endpoint: 5 year OS, assuming HR 0.75 with 80% power and type 1 error of 0.05 (2-sided), 1588 patients need to be randomised.

The Belgian ASPIRIN trial is part of a collaboration with the Dutch ASPIRIN trial. In total 1588 patients need to be randomised. Four hundred of these patients will be part of the Belgium trial. See 7.5 for more information about the collaboration.

4. INTRODUCTION AND RATIONALE

Epidemiology

Colorectal cancer is one of the most common cancers in developed countries, with about one million new cases each year and a mortality rate of nearly 33% (Cunningham et al., 2010). For both men and women, in Europe colorectal cancer is the second cause of cancer death. In Europe, in 2012 there were 447.000 new colorectal cancer patients and 215.000 patients died of colorectal cancer (Ferlay et al., 2014).

In Belgium colorectal cancer is the 2nd and 3rd cause of cancer-related death in males and females respectively. In 2013 there were 8406 new patients diagnosed with colorectal cancer and the incidence rate increased with almost 30% from 2004 till 2013 (Belgian Cancer Registry, 2013). The 5-year overall survival is approximately 66-67% and the incidence is expected to increase in the near future. The cornerstone of treatment for CRC is surgical resection. Adjuvant chemotherapy is recommended for TNM classified stage III and IV patients and for high risk stage II patients. Despite encouraging advances in surgical techniques and improved therapeutic protocols, studies have reported that on estimate 20%-35% of stage II-III patients eventually relapse and die from metastatic disease.

Initial therapy after diagnosis usually comprises primary surgical resection. When there is evidence of nodal involvement patients often receive adjuvant chemotherapy following initial surgery in an attempt to prevent metastatic spread (Cunningham et al., 2010). 50-60% of patients diagnosed with colorectal cancer eventually develop metastasis (National Comprehensive Cancer Network, 2014). Approximately 35% of patients presenting with stage III, 20% of patients with stage II, and 5 to 10% of patients with stage I cancer eventually relapse and subsequently die from metastatic disease (Goodwin & Asmis, 2009).

Adjuvant therapy in colon cancer

Surgical resection remains the corner stone of colon cancer treatment. For patients with an indication for adjuvant treatment, the combination of 5-fluorouracil and leucovorin or capecitabine and oxaliplatin (FOLFOX or CAPOX) is the current standard of care (College of Oncology, 2014; Goodwin & Asmis, 2009). The MOSAIC trial randomised 2246 patients with stage II or III colon carcinoma between 5FU/LV or 5-FU/LV+oxaliplatin. Results of this trial showed an increase in disease-free survival at 3 years from 72.9 to 78.2% ($p = 0.002$) for the addition of oxaliplatin to FU/LV. Five-year disease-free survival remained significant (HR: 0.80; $p = 0.003$) and at 6 years there was an overall survival benefit for stage III patients (68.3% versus 72.9%). The addition of oxaliplatin to LV5FU2 was associated with an increase in neutropenia, febrile neutropenia and neuropathy (Marshall et al., 2007).

In the current guidelines for Belgium (Alberts et al., 2012; Het Federaal kenniscentrum voor Gezondheidszorg, 2014; Van Cutsem et al., 2009), adjuvant chemotherapy is recommended for stage III colon cancer. In fit patients, fluoropyrimidine and oxaliplatin is the combination of choice (Alberts et al., 2012; Het Federaal kenniscentrum voor Gezondheidszorg, 2014). In October 2013 the screening program for colorectal cancer in Belgium started. According to the guidelines of the European Union the first phase of this program is for both men and women in the age group 56-74 years. In a next phase, the decision will be made to include also the age group 50-55 years. The results of the first phase of the screening program state that there are about 6 persons on 1000

participants who developed a colorectal cancer in situ and 7 persons out of 1000 participants developed invasive colorectal cancer (Bevolkingsonderzoek dikkedarmkanker, 2015). This detection limit is between 1.8% and 9.5% in accordance with the European Guidelines for population screening using immunochemical fecal occult blood test (iFOBT) (EU Guidelines & Crotta et al. 2004; Grazzini et al. 2004; Fenocchi et al. 2006; Saito).

Acetylsalicylic acid and cancer

Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) have shown to be effective in the prevention of colorectal cancer. Evidence for the role of acetylsalicylic acid as an anti-cancer agent comes from large trials primarily assessing the cardiovascular benefits of daily acetylsalicylic acid. In a pooled analysis of 5 large trials it was recently shown that acetylsalicylic acid taken for several years at doses of at least 75 mg daily reduced long-term incidence and mortality due to colorectal cancer (Rothwell et al., 2010).

In another meta-analysis acetylsalicylic acid was shown to significantly reduce adenoma formation in patients with a history of colorectal cancer (Cole et al., 2009).

Indirect evidence for acetylsalicylic acid as an adjuvant therapy comes from a report from Chan *et al*. In a non-randomised study they found that regular users of acetylsalicylic acid after the diagnosis of colorectal cancer had a reduced colorectal cancer-specific mortality (HR 0.71, 95% CI: 0.53-0.95) (Chan, Ogino, & Fuchs, 2009).

These data are very similar with data from our own study. In a large retrospective series of 4481 patients with colon cancer we found that acetylsalicylic acid use initiated after the diagnosis colon cancer was associated with a significantly increased overall survival (adjusted RR 0.61 (95%CI 0.46-0.81; p=0.001) (Bastiaannet et al., 2012).

In a third population based study from Scotland, the same conclusion was reached. In 2990 patients, acetylsalicylic acid use post-diagnosis was associated with a lower risk of all-cause mortality (HR 0.67, 95% CI: 0.57-0.79) (McCowan, Munro, Donnan, & Steele, 2013). Increasing age at diagnosis was also associated with increased risk reduction.

In contrast a fourth study by Walker *et al*. showed a more modest risk reduction of 9 percent (HR 0.91. 95% CI: 0.84-0.98). Subgroup analysis showed that the benefit was confined to those patients who also used acetylsalicylic acid before the diagnosis (Walker, Grainge, & Card, 2012). Again, in the report by Walker *et al*. the effect of acetylsalicylic acid seemed stronger in older patients and in colon cancer patients.

In recent publications from Chan *et al.* and Liao and co-workers, using the same cohort, acetylsalicylic acid use was associated with longer survival in PTGS2 expressing tumours and *PIK3CA* mutated tumours only. In that study, the hazard ratio for cancer related death was even 0.18 (95% CI 0.06-0.61), but only in tumours harboring a *PIK3CA* mutation (Liao et al., 2012). These results were validated by Domingo *et al*. where *PIK3CA* mutations were predictive for acetylsalicylic acid benefit (Domingo et al., 2013). Interestingly, this study was not able to validate the predictive value of PTGS2 expression.

The magnitude of the clinical benefits seen with acetylsalicylic acid in colorectal cancer seem to be larger, for example in Peter Rothwell's data, than could be explained by an effect on the approximately 15% of colorectal tumours with mutated *PIK3CA*. It is therefore unlikely that all effects of acetylsalicylic acid can be explained by this one mutation.

Acetylsalicylic acid use has also been associated with a decreased risk of developing a colorectal tumour with an intact *BRAF* gene but no association between post-diagnosis acetylsalicylic acid use, *BRAF* mutation status and clinical outcome has been found (Nishihara et al., 2013)

Recently, our group was not able to validate the predictive value of *PIK3CA* mutations and PTGS2 expression with low-dose acetylsalicylic acid, but did find a survival benefit with acetylsalicylic acid in tumours expressing HLA class I antigen only (Reimers et al., 2014). Altogether, these data indicate that in subgroups of patients the effect may be larger than in others, however, the findings remain inconsistent. A trend towards multifactorial approach of the etiology and treatment of colorectal cancer is ongoing. Not just isolated biomarkers seem to determine prognosis but molecular subtyping of tumours will be the future. This can also be helpful in developing new agents for the treatment of colorectal cancer (Linnekamp, Wang, Medema, & Vermeulen, 2015).
Currently three other trials are studying the effect of acetylsalicylic acid as adjuvant treatment in colorectal cancer. The ASCOLT trial in Singapore is a randomised, placebo-controlled trial studying the effect of acetylsalicylic acid 200 mg in patients with Dukes B and C colorectal tumour. The ALASCCA trial, currently under development, will be carried out in Sweden, and studies the effect of 80 mg acetylsalicylic acid in patients with *PIK3CA* mutated colorectal tumours.
In the near future the Add-Aspirin trial, carried out in India and the United Kingdom, will start including patients. This trial will randomise patients with different types of cancer for acetylsalicylic acid vs placebo treatment. Patients with upper gastro intestinal tumours, breast cancer, prostate cancer and colorectal cancer are eligible for inclusion.
Very recent new retrospective data again report that in parallel to the chemo preventive action of acetylsalicylic acid, this cheap and well tolerated drug is also implicated in prevention of distant metastases (Algra & Rothwell, 2012; Rothwell et al., 2012a; Rothwell et al., 2012b). These data from Rothwell indicate that acetylsalicylic acid might help in treatment of some cancers and provides proof of principle for pharmacological intervention specifically to prevent distant metastasis. Nevertheless, there is an urgent need for more randomised trials to prove the role of acetylsalicylic acid in the adjuvant treatment of cancer.

The mechanism by which acetylsalicylic acid exerts its activity is not completely understood. The protective activity of acetylsalicylic acid has been attributed to direct inhibition of the prostaglandin-endoperoxide synthase (PTGS), also known as cyclooxygenase (COX), family of enzymes involved in prostaglandin synthesis. The PTGS2 enzyme is strongly and rapidly induced in response to mediators of inflammation, growth factors, cytokines, and endotoxins; and its expression correlates with increased cell proliferation and tumour promotion (Herschman, 1996). Acetylsalicylic acid can decrease the production of potentially neoplastic prostaglandins arising from PTGS2-mediated catalysis of arachidonic acid (Vane, 1971). However, acetylsalicylic acid has a much broader range of downstream effectors, such as NF-KB, insulin-like growth factor I (IGF-I) and many others, as well as the inhibition of Wnt signaling and stem cell growth possibly as the result of enhanced beta-catenin (Dihlmann, Klein, & Doeberitz, 2003; Dihlmann, Siermann, & von Knebel, 2001; Wang et al., 2006).
Cancer is a heterogeneous disease encompassing differentiated cell types but also less committed stem-like cells. Recent evidence suggests that a subpopulation of tumour cells with distinct features such as self-renewal and the ability to differentiate into multiple lineages is responsible for tumour initiation, invasive growth and possibly dissemination to distant organ sites. The acquired ability of a cell to resist to apoptosis is a hallmark of almost all types of cancer. Recently, it has been shown that IL-4 expression is essential for the resistance to DNA damage-induced apoptosis of colon cancer stem cells (CSCs) (Todaro et al., 2007). CSCs are also resistant to the cytotoxic effect of chemotherapy. It has been shown that IL-4 confers colon CSCs with resistance to apoptosis (Todaro et al., 2007). Consistently, treatment with IL-4Ra antagonist or

anti-IL-4 neutralizing antibody strongly enhances the anti-tumour efficacy of standard chemotherapeutic drugs through selective CSCs sensitization. Notably, acetylsalicylic acid inhibits IL-4 gene expression (Cianferoni et al., 2001).
Based on the above observations, it is plausible that acetylsalicylic acid may both act as a preventive agent in CRC onset by modulating the Wnt pathway in CSCs, but also as adjuvant treatment by increasing CSCs' sensitivity to conventional chemotherapy regimens.

Acetylsalicylic acid and (non-) polyposis syndrome

Patients with (non-) polyposis syndrome are not eligible for inclusion in this trial. These patients have a different prognosis and different tumour characteristics (Brixen, Bernstein, Bulow, & Ehrnrooth, 2013; Myrhoj et al., 1997; Stigliano et al., 2008).
Additionally, the CAPP2 trial has examined the effect of 600 mg acetylsalicylic acid vs placebo in patients with Lynch syndrome plus previously affected patients within families meeting the Amsterdam criteria. This is the first large scale genetically targeted chemoprevention trial, which randomly assigned 861 participants to acetylsalicylic acid or placebo. Results showed when acetylsalicylic acid is used for at least two years, cancer incidence is reduced by 63% (IRR 0.37, 95% CI 0·18–0·78, p=0·008) (Burn et al., 2011). At this moment the CAPP3 trial is investigating the optimum low-dose acetylsalicylic acid to administer in at least 3000 gene carriers (Burn, Mathers, & Bishop, 2012). By excluding patients younger than 45 years, patients with a high a priori chance of (non-) polyposis syndrome are excluded.

Risk-benefit

Acetylsalicylic acid, even at low-doses appropriate for cardiovascular risk management, roughly doubles the incidence of gastric bleeding, and one or two people in every thousand are likely to have a bleeding every year. This risk rises with age and in people older than 80 years, it might be as high as seven per 1000 people every year (Elwood, Gallagher, Duthie, Mur, & Morgan, 2009). Age specific changes in the risk-benefit ratio of the preventive role of acetylsalicylic acid remain unclear. Data on the risk-benefit ratio for cancer prevention are insufficient and no definitive recommendations by a recent international consensus statement could be made regarding the preventive use of acetylsalicylic acid (Cuzick et al., 2009).
However, the demonstration of a significant therapeutic effect of acetylsalicylic acid as adjuvant treatment will alter the balance of risk and benefit importantly. The data from Chan et al., our own data and many more observational studies show a reduction of all-cause mortality (thereby including any fatal bleeds) up to 30 % (Bastiaannet et al., 2012; Chan et al., 2009; Chia, Ali, & Toh, 2012; Reimers et al., 2014). This potential benefit of acetylsalicylic acid is therefore additional to the risk-benefit equation in which the risk of bleeding is already offset by other benefits of acetylsalicylic acid i.e. prevention of ischemic stroke, myocardial infarction.

Relevance

The currently limited testing of acetylsalicylic acid as a therapeutic agent in the adjuvant setting, is in marked contrast to the numerous studies that were initiated using selective PTGS2 inhibitors before 2004.

And, with recent high profile failures of adjuvant bevacizumab and cetuximab in resected CRC, findings of a potential adjuvant benefit with acetylsalicylic acid, is not only timely, but highly important. Acetylsalicylic acid is an unlikely anti-cancer drug, however if proven beneficial, has the potential to change treatment paradigms, with significant global health and socio-economic impact. Because acetylsalicylic acid is off-patent and costs a-penny, development of acetylsalicylic acid as an anti-cancer therapy will be critically dependent on public funding and collaborative support from academia. In an era of escalating cancer treatment costs, providing the evidence for cost-competitive solutions must also be a necessary strategy and imperative. In this process, acetylsalicylic acid should not be over looked because it is neither new nor expensive.

Finally, there is data indicating that subgroups of patients harboring tumor with specific genetic mutations (e.g. PIK3CA, BRAF, RAS) may have a greater benefit than others (Cianferoni et al., 2001; Cunningham et al., 2010; Cuzick et al., 2009; Dihlmann, Klein & Doeberitz, 2003; Dihlmann, Siermann & von Knebel, 2001; Domingo et al., 2013). The goal of the study is to assess PIK3CA, BRAF and RAS prospectively. These analyses will then be correlated with overall survival and disease-free survival with appropriate methods (Cox Proportional Hazard Model) and adjustment and possible confounding factors.

Key points

- The number of colon cancer patients is increasing and there is a strong need for therapeutic improvement
- The colorectal cancer screening in Belgium has raised the incidence
- Pre-clinical, epidemiological and clinical data demonstrate that acetylsalicylic acid use is associated with improved colon cancer outcome
- Demonstration of a significant therapeutic effect of a well-tolerated drug that costs mere pennies per day would be a major clinical advance

5. OBJECTIVES

Primary Objective:

- To study the effect of 80mg acetylsalicylic acid (given orally once daily for 5 years) on 5 year overall survival (OS) for stage II and III colon cancer patients

Secondary Objective(s):

- To study the effect of acetylsalicylic acid on 3 year disease free survival (DFS)
- To study the effect of acetylsalicylic acid on time to treatment failure (TTF)
- To study the effect of acetylsalicylic acid on toxicity, for example the interaction of acetylsalicylic acid with chemotherapy

Tertiary Objective (s):

- Genetic analysis on surgical specimen from all patients: PIK3CA, BRAF and RAS mutation analysis
- Evaluation of therapeutic compliance (using a diary on paper and/or via smartphone) and patient reported outcomes (using a web-based customized survey with patient access)
- Define subpopulations with greater adjuvant benefit using acetylsalicylic acid

6. STUDY DESIGN

A phase III double-blind placebo-controlled randomised trial is proposed. Stage II and III colon cancer patients with or without adjuvant chemotherapy will be randomised between low-dose acetylsalicylic acid (80 mg) or placebo, within 12 weeks after radical resection. Treatment will start at least 10 days after surgery. Study medication will be continued for 5 years. The research question will be addressed in patients with and without adjuvant chemotherapy by means of two parallel studies.

Trial timelines

Patient inclusion in Belgium starts from 2017 till 2021. The follow-up period for every patient is 5 years. Collection point of all data is scheduled in 2026-2027.

Stratification factors:

- Stage in the 'no adjuvant chemotherapy' arm
- Age <70 years and ≥70 years

Diary

All patients, with or without adjuvant treatment, get the chance to fill out a diary for the therapy compliance.

Biobanking:

15 slides of the surgical resection specimen of the primary tumour will be requested by the biobank of UZA from the hospitals where the patients received surgical treatment. The slides will be stored in the biobank of the UZA until needed for downstream analysis of molecular biomarkers as described in the tertiary objectives above in this protocol. After DNA isolation and biomarker testing the left-over of the DNA will be stored in the biobank until maximum 30 years after the end of the study. Furthermore, data will be stored in the IT-platform regarding the surgical specimen. The individual results of the genetic analysis will be conserved. The patients give permission for the use of their clinical resection specimen and genetic testing by signing the informed consent (IC).

Questionnaire (QLQ-C30, ADL, IADL)

User-friendly electronic communication has proven feasible for treatment intake (Rasschaert et al., 2016) and would further allow to prospectively evaluate patient reported outcomes (PROs) such as quality of life measures and questionnaires like PRO-CTCAE (Kluetz, Chingos, Basch, & Mitchell, 2016) who are looking at gastro-intestinal bleeding or risk thereof. The self-reported questionnaires used in this study will measure the quality of life (QLQ-C30), activities of daily life (ADL), and instrumental activities of daily living (IADL). The questionnaires will be offered to the patients electronically (via email) or on paper, and will take approximately 20 minutes to complete. The paper questionnaires are processed by the UZA research team. The data from the electronic questionnaires are processed by order of UZA, on the instruction of the principal investigator, by Remedus BVBA, a service company for home care and home hospitalization (Boomsesteenweg 44, 2630 Aartselaar). For this, Remedus BVBA has concluded a processing agreement with UZA in accordance with the applicable General Data Protection Regulation (GDPR).

To be able to process the data from the electronic questionnaires, the study patient must complete the "Application form for the Aspirin Trial". By completing this application form the patient agrees that Remedus BVBA will process his/her personal data including name, date of birth, national register number, home address, telephone number and email address.

Web-based customized system

Since the beneficial effect of acetylsalicylic acid is due to its chronic use by motivated patients, further evaluation of therapeutic compliance is important. The local investigator team is free to choose if they want to be engaged in the sub-study 'AMTRA' (Ambulant Monitoring of cancer Therapy using a smaRtphone Application). In this sub-study, only patients receiving adjuvant chemotherapy have the option to complete an additional questionnaire during the first 6 months. Patients will be questioned daily for the intake of study medication and symptomatic toxicity scores through an interactive email-based communication alongside physician reported CTCAE grades (at the follow-up visits) to obtain information about treatment tolerability. The 29 questions are adapted to the personal situation of the patient (e.g. type of chemotherapy). In this interactive system Remedus provides a mobile application 'RemeCoach' that the patients can download for free on their own smartphone. If any toxicity occurs, the physician will be informed quickly and advice can be given on –for example- taking analgesic medication or pills for diarrhea and so on. After six months the patient can decide whether he/she wants to continue the follow-up via the mobile application (free of charge) or not. Continuing the follow-up after six months is only possible if the principal investigator agrees.
If the patient wishes to participate in AMTRA, he/she agrees that Remedus BVBA will process his/her personal data (name, date of birth, telephone number, email, address) as well as the registrations in the smartphone application.

All registrations will be monitored in an interactive email based communication system (RemeCare platform) by the central study coordinator. The RemeCare platform is also one of the services of Remedus BVBA. This IT-platform, the storage of personal data and the exchange with the electronic patient dossier is approved by the privacy commission of Belgium (CBPL).

The patients will be informed by Remedus about this process. A Remedus nurse will visit the patient's home once to explain the application. Once the procedure has become routine, the local investigator will inform the patients about the mobile application. However, the patients are able to contact Remedus by phone at any time to report technical problems or to ask questions about the use of the mobile application. During the follow-up visits, information about the treatment tolerability will be assessed.

Patients without adjuvant chemotherapy, or patients receiving adjuvant chemotherapy who don't want to participate in the sub-study AMTRA, will get a paper patient diary in which side effects and the intake of medication can be registered. If the local investigator doesn't want to be engaged in the sub-study AMTRA, all study subjects will receive the paper patient diary.

7. STUDY POPULATION

7.1 Population

- Patients with stage II or III colon cancer, 45 years of age and older after radical (R0) resection will be randomised
- Patients will be recruited from different Belgian hospitals (target number: 400)

7.2 Inclusion criteria

- Patients 45 years and older
- Patients with histologically confirmed adenocarcinoma of the colon
- Patients must have TNM stage that is one of the following: pT3-4; N0-2 and M0, or pT1-2 and N1-2 (UICC stage II and III) (in case of >1 tumour: more advanced tumour is stage II or III)
- Patients who have undergone curative radical resection (R0 resection) within 12 weeks prior to study entry
- Written informed consent according to national and local regulation

7.3 Exclusion criteria

- Patients with rectal cancer (defined as tumour within 15 cm from the anal verge)
- Patients currently taking (low-dose) acetylsalicylic acid or other anti-aggregantia for any reason
- Patients currently taking oral anti-coagulants or use of LMWH or use of DOACs
- Patients with a history of bleeding disorders or active gastric or duodenal ulcers
- Patients currently taking high dose systemic glucocorticoids. (≥ 30 mg predniso(lo)n or equivalent)
- Patients with (suspected) (non-) p olyposis syndrome (FAP/AFAP, MAP, Lynch syndrome)
- Patients with >100 polyps of the colon **or** a known hereditary syndrome of the colon in a first degree family member (father/mother/brother/sister/son/daughter)
- Allergy or intolerance to salicylates
- Patients with local or distant recurrent disease
- Previous malignancies other than CIN, BCC or SCC with a disease free survival *less than* 5 years
- Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

7.4 Sample size calculation

Overall Survival

The sample size calculation was performed on Overall Survival with the assumption that acetylsalicylic acid will increase Overall Survival with a hazard ratio of 0.75 in the acetylsalicylic acid group versus placebo (in our retrospective study the *upper* limit of the confidence interval in older patients was 0.78 (Bastiaannet et al., 2012). The study will consist of two parallel studies in patients who do and do not receive adjuvant chemotherapy (see flow chart Aspirin trial, chapter 3). These two arms will be powered separately as we aim to achieve significant results in both trials. The calculations relate to the trial in Belgium and the one in The Netherlands.

- **Sample size in patients who receive no chemotherapy.**

The number of events needed in this population was calculated used the next formula:

$d = (1.96 + z_{\beta})^2 \ (\delta+1 \ / \ \delta-1)^2$ where $\beta=0.8$ and $\delta=0.75$.

Overall, the calculation showed that 384 events are needed; so in the control group 219 events are needed. In the life tables of patients who received no chemotherapy 912 events were observed in 1809 patients in 6.5 years. To observe the 219 events in 6.5 years we need to include 219/(912/1809) = 434 patients per arm with a total of **868 patients**.

- **Sample size in patients who do receive chemotherapy**

In the life tables of the patients who received chemotherapy 204 events were observed in 335 patients in 6.5 years. To observe the 219 events in 6.5 years in this trial we need to include 219/(204/335) = 360 patients per arm with a total of **720 patients**.

In conclusion, sample size calculation showed that an inclusion of in total **1588 patients** will be sufficient to detect a hazard ratio of 0.75. Data of the study population in The Netherlands and the study population in Belgium will be pooled for analysis. (Target number in Belgium: 400 patients).

7.5 International Collaboration

7.5.1 Collaboration between LUMC and UZA

Several hospitals in the surroundings of Antwerp will participate in the ASPIRIN trial (NL 38132.058.14). In the end of 2015 the first meeting between Leiden University Medical Center and Antwerp University Hospital was organised to discuss the expansion of the ASPIRIN trial to Belgian hospitals. The rationale for this collaboration is to accelerate accrual, because finalising the trial within the timeframe is highly important. For both countries separate protocols are in place, since the Belgian trial has several additional side studies implemented which will not take place in the Netherlands. Nonetheless, both protocols are similar in a way that allows the data to be pooled for analysis. One database will be used to collect all data for both countries, central data management will be performed by Datacenter Department of Surgery of the LUMC in Leiden, The Netherlands.

7.5.2 Collaboration with the Add-Aspirin trial

The MRC clinical trial unit in the United Kingdom is ongoing in the development of the 'Add-Aspirin' trial. In collaboration with this group it was agreed in principle that patients in both trials will be shared after both trials are analysed and published separately. The expected accrual in the UK is 2300 colorectal cancer patients older than 18 years. These patients will be randomised for high-dose acetylsalicylic acid, low-dose acetylsalicylic acid or placebo for 5 years. Assuming comparable demographics and incidence of colon cancer, data from approximately 400 patients can be shared.

8. TREATMENT OF SUBJECTS

8.1 Investigational product/treatment

Patients will be randomised to either receive orally acetylsalicylic acid 80 mg once daily or placebo.

8.2 Concomitant medication

Patients are allowed to use their concomitant medication in consultation with their treating physician. Concomitant medication is defined as (1) any medication that is taken for ≥ 3 months, and obtained on prescription, or (2) any medication that is considered relevant by the treating physician. Concomitant medication use will be documented with every follow-up visit after the start of the treatment. Patients who need to undergo elective surgery or other interventional procedures do not have to stop taking the study drug. Evidence suggests that acetylsalicylic acid use prior to and after surgery does not increase (post) operative bleeding risk (Sahebally, Healy, Coffey, & Walsh, 2014). In case a specific situation (e.g. a procedure at the dentist) requires stopping study medication, the patient may stop 7 days prior to the procedure. Recommence of study medication is directly after recovery, if clinical condition allows.

8.2.1 Gastroprotection

Systematic prescription of proton pump inhibitors (PPI's) for patients taking low-dose aspirin is not recommended in the absence of high risk GI-bleeding. On the other hand, PPI's are recommended in patients taking low-dose aspirin in the following 3 cases: history of peptic ulcers or GI-bleeding or concomitant NSAID medication or Helicobacter Pylori infection. However, the ASPREE study (ASPREE Investigator Group, 2013) (ASPirin in Reducing Events in the Elderly) safely enrolled 19.000 patients above 70 years of age in Australia. In this study where patients were randomised for low-dose acetylsalicylic acid (100 mg) or placebo, PPI's were not routinely advised as concomitant medication (Prof. Dr. M. Nelson, personal communication). Also in the before mentioned ASCOLT-study (Ali R, 2011) (NCT00565708) and Add-Aspirin study (ISRCTN74358648) standard PPI use is not recommended.

If dyspeptic symptoms do occur we recommend to cease the study medication for a period of 14 days, and then re-challenge. If symptoms recur, the treating physician may add other medication (e.g. a PPI). Gastroprotection is advised in patients who chronically use NSAID's, systemic glucocorticoids, SSRI, venlafaxine, duloxetine, trazodon or spironolactone. Also in case of severe incapacitating rheumatoid arthritis, heart failure or diabetes, standard PPI's may be considered.

8.2.2 Chemotherapy

Concomitant use of chemotherapy and acetylsalicylic acid is allowed. When patients are treated with chemotherapy and thrombocytopenia is observed, study treatment may be discontinued until thrombocytes reach an acceptable (according to the treating oncologist) level for the re-administration of the study drug. The study drug may be restarted after the completion of chemotherapy, even if chemotherapy duration exceeds the maximum period of study drug interruption (see 10.4.1 Specific criteria for withdrawal)

9. INVESTIGATIONAL MEDICINAL PRODUCT

9.1 Aspirin

Aspirin, also known as acetylsalicylic acid is a salicylate often used as an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever, and as an anti-inflammatory medication. Salicylic acid, the main metabolite of acetylsalicylic acid, is an integral part of human and animal metabolism. While much of it is attributable to diet, a substantial part is synthesized endogenously. Acetylsalicylic acid also has an antiplatelet effect by inhibiting the production of thromboxane, which under normal circumstances binds platelet molecules together to create a patch over damaged walls of blood vessels. Because the platelet patch can become too large and also block blood flow, locally and downstream, acetylsalicylic acid is also used long-term, at low-doses, to help prevent heart attacks, strokes, and blood clot formation in people at high risk for developing blood clots (Lewis et al., 1983). It has also been established that low-doses of acetylsalicylic acid may be given immediately after a heart attack to reduce the risk of another heart attack or of the death of cardiac tissue. Acetylsalicylic acid is part of a group of medication called non-steroidal anti-inflammatory drugs (NSAIDs). Though acetylsalicylic acid, and other salicylates have similar effects (antipyretic, anti-inflammatory, analgesic) and inhibit the same enzyme cyclooxygenases their mechanism of action, acetylsalicylic acid does it in an irreversible manner. For example, NSAIDs antiplatelet effects last in the order of hours, whereas acetylsalicylic acid's effect lasts for days (until the body replaces the suppressed platelets).

Kinetics: Resorption: orally 80–80%. T_{max} = ½–2 hours.
Metabolism: in the liver, but also in plasma.
Elimination: with urine as metabolites and unchanged acetylsalicylic acid (1%).

9.2 Summary of findings from non-clinical studies

Acetylsalicylic acid inhibits prostaglandin-endoperoxide synthase 2 (PTGS2), also known as cyclooxygenase-2 (COX-2)(Chan et al., 2009). PTGS2 is an inducible enzyme whose expression and activity are up-regulated in response to a variety of cytokines, growth factors, and tumour promotors. PTGS2 was shown to be up-regulated in colorectal adenomas and adenocarcinomas (Sheng et al., 1997). Approximately, 70% of colorectal tumours express PTGS2, which increases with stage (Midgley et al., 2010). PTGS2 plays an important role in colorectal carcinogenesis, invasion, angiogenesis and metastasis. The importance of PTGS in tumourigenesis was established by knockout of the PTGS2 gene in mice containing a truncating mutation in the adenomatous polyposis coli (APC) gene. These mice developed markedly fewer intestinal adenomas than did APC-mutated mice with intact PTGS2 (Oshima et al., 1996). Several studies showed that this PTGS2 effect can be reversed by selective PTGS2 inhibitors (Chen et al., 2001).

9.3 Summary of findings from clinical studies

Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) have shown to be effective in the prevention of colorectal cancer. However, results from the Victor trial, a phase III randomised trial assessing rofecoxib in the adjuvant setting of colorectal cancer, demonstrated no difference in overall survival (McIlhatton et al., 2011; Midgley et al., 2010).

Previous studies showed that regular use of acetylsalicylic acid was associated with a lower risk of colorectal cancer (Chan et al., 2009; McIlhatton et al., 2011). A recent study in patients with stage I-III colorectal cancer selected from two nationwide health professional cohorts in the U.S. showed that regular acetylsalicylic acid use after the diagnosis of colorectal cancer compared with non-users is associated with a lower risk of colorectal cancer-specific and overall mortality (adjusted Hazard Ratio(HR) 0.71), especially among individuals with tumours that overexpress PTGS2 (adjusted HR 0.39)(Penning et al.). Another study where pre-diagnosis non-steroidal anti-inflammatory drug use and survival after diagnosis of colorectal cancer was evaluated, showed a higher reduction in colorectal cancer mortality risk after diagnosis by acetylsalicylic acid use than overall NSAID use (Coghill et al., 2011). The magnitude of effect of acetylsalicylic acid in a large Scottish cohort (14) (N=2.990) on all-cause mortality (adjusted HR 0.67, 95% CI 0.57–0.79) was more marked than that seen in the Dutch study by Bastiaannet *et al*. (Bastiaannet et al., 2012) (HR 0.77, 95% CI 0.63–0.95) and for colorectal cancer mortality (adjusted HR 0.58, 95% CI 0.45–0.75) than Chan *et al.* (HR 0.79, 95% CI 0.53–0.95) (Penning et al.). Recently, subgroup analysis in a Dutch cohort of elderly patients (75 and older) who received no chemotherapy the survival gain was especially large (adjusted RR 0.52 (95% CI 0.35-0.78), p=0.001)(Bastiaannet et al., 2012).

An important addition to our current understanding of the anticancer effect of acetylsalicylic acid is a meta-analysis involving 17.285 persons from 5 randomised trials assessing the effect of acetylsalicylic acid to prevent cardiovascular events (Liao et al., 2012). Allocation to acetylsalicylic acid reduced the risk of death due to cancer in patients who developed adenocarcinoma, particularly in those without metastasis at diagnosis (HR 0.50 95% CI: 0.34-0.74).

Since all data on the use of acetylsalicylic acid as an adjuvant treatment are retrospective cohort studies or from trial designed for cardiovascular risk management, the magnitude of effect on all-cause and cancer specific mortality remains an open question. But, combining all available data, an assumption of 25% risk reduction for all-cause mortality, in patients with colon cancer only seems a conservative estimation.

9.4 Summary of known and potential risks and benefits

9.4.1 Gastrointestinal

Acetylsalicylic acid use has shown to increase the risk of gastrointestinal bleeding. Combining acetylsalicylic acid with other NSAIDs has also shown to further increase this risk. Using acetylsalicylic acid in combination with clopidogrel or warfarin also increases the risk of upper gastrointestinal bleeding. In addition to enteric coating, "buffering" is the other main method companies have used to try to mitigate the problem of gastrointestinal bleeding. Buffering agents are intended to work by preventing the acetylsalicylic acid from concentrating in the walls of the stomach, although the benefits of buffered acetylsalicylic acid are disputed.

9.4.2 Central effects

Large doses of salicylate, a metabolite of acetylsalicylic acid, have been hypothesized to cause tinnitus based on experiments in rats, via the action on arachidonic acid and N-methyl D- aspartate receptors cascade.

9.4.3 Hives and swelling

For a small number of people, taking acetylsalicylic acid can result in symptoms that resemble an allergic reaction, including hives, swelling and headache. The reaction is caused by salicylate intolerance and is not a true allergy, but rather an inability to metabolize even small amounts of acetylsalicylic acid, resulting in an overdose.

9.4.4 Other effects

Acetylsalicylic acid can induce angioedema in some people. Acetylsalicylic acid causes an increased risk of cerebral microbleeds. Such cerebral microbleeds are important since they often occur prior to ischemic stroke or intracerebral hemorrhage, Binswanger disease and Alzheimer's disease. Acetylsalicylic acid can cause prolonged bleeding after operations for up to 10 days.

Other cardiovascular complications are also possible. Based on scientific evidence the patients will be advised to take the study medication during or after the evening meal. By taking the aspirin in the evening, the platelet reactivity will be reduced in the morning, which may be associated with less adverse cardiovascular events (Bonten et al., 2015).

9.4.5 Precautions

Acetylsalicylic acid should not be taken by people who are allergic to ibuprofen or naproxen, or who have salicylate intolerance or a more generalized drug intolerance to NSAIDs, and caution should be exercised in those with asthma or NSAID-precipitated bronchospasm. Owing to its effect on the stomach lining, manufacturers recommend people with mild diabetes seek medical advice before using acetylsalicylic acid. Even if none of these conditions is present, there is still an increased risk of stomach bleeding when acetylsalicylic acid is taken with alcohol. Acetylsalicylic acid is known to cause hemolytic anemia in people who have a genetic disease glucose-6-phosphate dehydrogenase deficiency (G6PD), particularly in large doses and depending on the severity of the disease. Use of acetylsalicylic acid during dengue fever is not recommended owing to increased bleeding tendency. In people with kidney disease, hyperuricemia, or gout caution must be taken because acetylsalicylic acid inhibits the kidneys' ability to excrete uric acid, and thus may exacerbate these conditions. Acetylsalicylic acid can increase of the activity of several drugs, such as sulfonylureumderivates, insulin, and acetazolamide, and the side effects of methotrexate.

9.4.6 Pregnancy

Regular use of aspirin may adversely affect a pregnancy and/or foetal development. Regular aspirin use whilst breast feeding can also cause complications in the neonate/infant and should be avoided. Therefore, participants joining the ASPIRIN trial should not be pregnant or breast feeding at registration and will be advised against becoming pregnant during the treatment period of the trial. If a participant becomes pregnant during the trial, the study drug should be stopped and the pregnancy should be reported on the 'Comment form'. This must also be discussed directly with the trial coordinator. Follow-up within the trial will continue.

9.4.7 Overdose

Acetylsalicylic acid overdose can be acute or chronic. In acute poisoning, a single large dose is taken; in chronic poisoning, higher than normal doses are taken over a period of time. Acute overdose has a mortality rate of 2%. Chronic overdose is more commonly lethal, with a mortality rate of 25%. Chronic overdose may be especially severe in children. Toxicity is managed with a number of potential treatments, including activated charcoal, intravenous dextrose and normal saline, sodium bicarbonate, and dialysis. The diagnosis of poisoning usually involves measurement of plasma salicylate, the active metabolite of acetylsalicylic acid, by automated spectrophotometric methods. Plasma salicylate levels generally range from 30–80 mg/L after usual therapeutic doses, 50–300 mg/L in patients taking high doses and 700–1400 mg/L following acute overdose.

9.5 Description and justification of route of administration and dosage

Following post-operative randomisation, patients will receive acetylsalicylic acid 80 mg or placebo orally for 5 years. Adequate instruction regarding dose and frequency of the study medication will be given to the patient. It is very important to emphasise that the patient may not take acetylsalicylic acid on their own during participation in the study. Depending on the randomization, this could remodel the results or the patient could take a double dose of the acetylsalicylic acid.

9.6 Dosages, dosage modifications and method of administration

Study medication can be taken during any moment of the day. However, to avoid gastric complaints, it is advised to take study medication during or just after a meal. In favor of less adverse cardiovascular events, the patients will be advised to take the study medication during or after the evening meal (Bonten et al., 2015). There will be no dose reduction for adverse events related to acetylsalicylic acid. Acetylsalicylic acid should be stopped if the patient develops an adverse event that is related to the study drug (toxicity). The drug will not be reintroduced in case of anaphylaxis, angioedema or gastrointestinal bleeding. Otherwise, re-introduction of the drug will be done after complete resolution of the adverse event following a rest period without study drugs (maximal duration 6 weeks). If the adverse event subsequently recurs, the patient will be taken off treatment with the study drug.

In case of observed thrombocytopenia when patients receive chemotherapy, it is allowed to interrupt study treatment according to the treating medical oncologist. Patients can restart the study drug after completion of chemotherapy or when thrombocytes reach an acceptable level according to the treating medical oncologist. The study drug may be restarted even if chemotherapy duration exceeds the 6 weeks (maximum period of study drug interruption) (see 10.4.1 Specific criteria for withdrawal).

9.7 Preparation and labelling of Investigational Medicinal Product

Preparation and labeling will be done according to relevant GMP guidelines. The acetylsalicylic acid 80 mg tablets and matching placebo tablets are manufactured by Tiofarma Beheer B.V. (Oud-Beijerland, the Netherlands). The Investigational Medicinal Product Dossier (IMPD) of the acetylsalicylic acid and placebo are provided by Tiofarma Beheer B.V. The medication is released by the Qualified Person of Tiofarma.

9.8 Drug accountability

Tiofarma is responsible for the manufacturing, packaging, labelling and shipment of the study medication, conform GDP. The local hospital pharmacy is responsible for accountability and distribution of the investigational product on patient's level.
Randomisation codes are kept strictly confidential and are accessible by authorised persons only.
At the end of the study, all used and unused containers/products must be destroyed on site as dictated by the appropriate standard procedures. Under no circumstances should the investigator or site personnel supply product to other investigators or clinics or allow the study supplies to be used otherwise than as directed by this protocol.

10. METHODS

10.1 Study parameters/endpoints

10.1.1 Main study parameter/endpoint

The primary endpoint is 5 year Overall Survival (5y-OS). The time to an event for OS is defined as the time interval between the date of randomisation and the date of death. A patient that is still alive at the last date of follow-up patient is censored for analysis and the time at risk corresponds to the time interval between the date of randomisation and the date of last follow up.

10.1.2 Secondary study parameters/endpoints

Two secondary endpoints:

- Disease Free Survival (DFS). The time to an event for DFS is defined as the time interval between the date of randomisation and the date of disease recurrence or death, whichever comes first. Recurrence of a disease can be a loco-regional recurrence, a distant recurrence or a new primary colon cancer. The evidence for recurrence must be documented in the patients' file. The date of radiological evidence, e.g. CT, MRI, etc, or colonoscopy will be considered as date of recurrence. An elevated carcinoembryonic antigen (CEA) level, as solitary finding, will not be considered acceptable evidence of colon cancer recurrence.
- Time to Treatment Failure (TTF). The time elapsed between randomisation until treatment discontinuation due to disease progression, unacceptable toxicity, death or any other event of interest.

10.1.3 Tertiary parameters

- Genetic analysis on surgical specimen from all patients in particular PIK3CA, BRAF and RAS mutation analysis
- Evaluation of therapeutic compliance and patient reported outcomes using a web-based customized survey with patient access
    - Therapeutic compliance information of both aspirin and chemotherapy, treatment regimen, medication dose, number of cycles
    - Patient reported outcomes:
        - Quality of life Questionnaire C30 (European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30; appendix 1)
        - Activities of Daily Living and Instrumental Activities of Daily Living (Modified ADL and IADL; appendix 2)
        - Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE v4.0; appendix 3) (Kluetz et al., 2016)
- Comprehensive assessment visits to evaluation of patient's function, cognition and safety
    - Geriatric Assessment Screening tool (G8; appendix 4)
    - Adult Comorbidity Evaluation comorbidities (ACE-27; appendix 5)
    - Social status (appendix 6)
    - (Serious) Adverse Events ((S)AE according to CTCAE v4.0 (National Institute of Health, 2010) (appendix 7)

- Define subpopulations with greater adjuvant benefit using acetylsalicylic acid

10.1.4 Other study parameters

Following patient and tumour characteristics will be documented:

- Identification of the patient: unique ASPIRIN study number, Dutch Surgical Colorectal Audit (DSCA) registration (see paragraph 14.3) number, sex and date of birth
- Comorbidities: cardiac, vascular, diabetes, pulmonary, neurological, gastrointestinal, urogenital, thrombosis, muscle and joints, endocrine diseases, infectious diseases and previous malignancies (also registered by the DSCA, see paragraph 14.3) Comorbidities will also be registered by using the Adult Comorbidity Evaluation-27 (ACE-27)
- Previous abdominal surgery
- Previous and current medication (registered by case report form (CRF))
- Diagnostics performed preoperative
- Treatment: pre-operative treatment, date of surgery, ASA-score, urgency of surgery, surgical procedure
- Histopathology: Histology, number of resected lymph nodes, number of positive lymph nodes, pathological TNM classification
- Adjuvant treatment: treatment regimen, dose, no. of cycles, reason no chemotherapy

A total of 15 slides of left-over tissues after surgery will be stored at the biobank of the UZA. After the trial this tissue material and/or DNA isolated from the tumour. The tissues will be used for biomarker investigation: *PIK3CA*, *RAS* and *BRAF* mutation analyses.
Therapy compliance and patient reported outcomes will be documented through the web-based customized survey with patient access (through email notification) or through paper questionnaires.

10.2 Randomisation and treatment allocation

10.2.1 Patient randomisation procedure

After having properly checked all eligibility criteria and having obtained patients informed consent, patients will be randomised online through the ProMISe program or by phone and/or email at UZA.

Online randomisation

Online randomisation will only be performed by the Study Coordinator of UZA during office hours after having received a completed randomization CRF (F01) from the local investigator team
A confirmation email with the patient specifications and the trial number will be automatically sent to the central study team, and the local study team (including the primary investigator, the local study coordinator, and the local hospital pharmacy). This confirmation email is blinded, i.e. the allocated treatment is not mentioned.

The result of the randomisation will only be visible in the electronic patient viewer (ProMISe) to the local pharmacist. In this way, he or she will be notified about the allocated treatment. In the process, only the local pharmacist(s) will be unblinded.

Randomisation by email and/or phone

Randomisation can also be done by email or phone. The Study Coordinator of UZA can be contacted during daytime by email (aspirin@uza.be) or by phone (+32 3 821 40 82). The central Study Coordinator can also be approached if there are questions or remarks.

The local investigator fills out the randomisation CRF (F01) and passes this CRF to the central study coordinator. During the randomisation procedure eligibility criteria will be checked/confirmed by the central study coordinator. After randomisation, a sequential identification number will be applied. This number has to be recorded on the randomisation form, along with the randomisation date. The randomisation form must be signed by the investigator and filed with the CRFs. An automatic email will be sent to the investigator to confirm the randomisation (see online randomisation).

10.2.2 Unblinding

The treatment will be unblinded in the following cases:

- End of the study, after the final analysis, prior to writing the publication
- In case of emergency (SAE to the patient possibly attributed to the study medication)
- In case of another indication that warrants acetylsalicylic acid treatment (e.g. cardiovascular incidents or a (non) polyposis syndrome that was diagnosed after inclusion in the study)

Because acetylsalicylic acid is prescribed in low dosage and is a drug with only a slight risk of causing immediate life threatening events, no 24-hour service is provided for deblinding. When deblinding is necessary, the local participating centre can provide deblinding the next work day. In case of an SAE which's treatment requires unblinding of the study treatment, there is a specific procedure that needs to be followed (see appendix 11).

10.3 Study procedures

The timelines of data collection, the tasks involved and the actors performing the tasks are shown in appendix 8.

10.3.1 Before treatment starts

After surgery, when the histology of the cancer and the disease stage is known, patients will be randomised for acetylsalicylic acid use or placebo within 12 weeks after surgery. Within a week after randomisation study medication must be started. Treatment with acetylsalicylic acid or placebo will start at least 10 days after surgery. In case of treatment with chemotherapy, study medication can be used concomitantly with chemotherapy.

Local investigator fills out baseline CRF (F02), in which the ACE-27, G8 Geriatric Assessment Screening tool, Social Situation, chemotherapy, and chronical use of concomitant medication are evaluated. Any medication that is taken for ≥ 3 months, and obtained on prescription, or any medication that is considered relevant by the treating physician must be listed in the concomitant medication part of the baseline CRF. Also, patients will be asked to fill in the questionnaires: QLQ-C30, modified ADL and IADL (Laan et al., 2014) on paper or through the web-based customized survey (cfr. Chapter 6. Study design).

10.3.2 During adjuvant therapy (years 1-5)

The follow-up period will be according to the national guidelines, but with a minimum of follow-up visits every 6 months the first 2 years, and every year in the third to fifth year. These **study visits** must be organized in **a time window of 8 weeks before until 8 weeks after** the fixed time points M6, 12, 18, 24, 36, 48, and 60.

At the time points M0, 6, 36, and 60, the patient will need to complete the QLQ C30, ADL and the IADL. These time points also coincide with a study visit. The **paper/electronic questionnaires** must be completed in **a time window of 8 weeks before until 8 weeks after** the fixed time points M0, 6, 36, and 60.

All other visits (≠ fixed study visit time points) that are relevant in the context of the patient's disease and/or the patient's participation in the study are considered as additional visits. Additional visits must be registered in the Follow-Up Form (F03) 'Additional Visit'.

In case the patient has one of the following events, special forms have to be completed:

- Recurrence/new primary form
- Concomitant medication form
- End of study treatment form
- Off study form
- Death form
- AE form
- SAE form

During the follow-up visits, information about the therapy compliance (grade), treatment tolerability (adverse events and grade), and concomitant medication will be assessed.

The local investigator team may choose whether or not to fill in the paper CRFs themselves. If not, the central study coordinator will perform this task on the condition that the participating center gives access to the medical records of the study patients. This is necessary to be able to fill in the paper CRFs (with the exception of Randomisation Form (F01), Baseline Form (F02) and SAE Form (F40) that will be completed by the local investigator team). Centers who are not able to permit the central study coordinator access to the medical record, have to fill in the paper CRFs themselves (cfr Chapter 14 guidelines).

Local investigator teams that complete the paper CRFs themselves, must upload these forms in a secure private Cloud.
The conversion of the paper CRFs into the electronic CRFs in the ProMISe database will be performed by the central study coordinator.

For more information about the study procedure, see study events table (appendix 8).

10.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

10.4.1 Specific criteria for withdrawal

- Patients who develop anaphylaxis, angioedema or gastrointestinal bleeding
- Recurrent disease
- Patients with diagnosed (non-) polyposis syndrome
- Intercurrent, cardiovascular disease that warrants acetylsalicylic acid or other anti-aggregantia treatment
- Patients that warrant treatment with oral anti-coagulants or use of LMWH or use of DOACs
- Greater than 6-week interruption in study drug administration due to toxicities (In case of thrombocytopenia when patients are treated with chemotherapy, study drug interruption may exceed 6 weeks)
- Unacceptable study drug toxicity
- Patient withdrawal of consent to continue treatment
- Intercurrent, non-cancer related illness that prevents continuation of therapy or regular follow-up
- Changes in a patient's condition that renders the patient not suitable for further treatment in the judgement of the investigator
- Major protocol violation or discovery of information that, if previously known, would have rendered the patient ineligible for study

10.4.2 Replacement of individual subjects after withdrawal

After withdrawal subjects will not be replaced.

10.4.3 Follow-up of subjects withdrawn from treatment

Subjects withdrawn from treatment will still be followed-up for 5 years and their data will be corrected later in the statistical analysis for the time they used the study drug.

10.5 Premature termination of the study

The study will be terminated when there is one of the following criteria:

- Serious adverse side effects related only to acetylsalicylic acid use in >5 % of the subjects
- If the results of the interim analysis do not show survival benefit for acetylsalicylic acid use or if these results show a survival gain for control group

10.6 Data collection and data storage

Clinical data are collected through the CRFs in a central database and management is performed by the Datacenter Department of Surgery of the LUMC in Leiden, The Netherlands. Patient reported outcomes are collected through questionnaires on a web-based customized survey meeting the requirements of the privacy commission. The results from the analysis of tumor tissues stored at the biobank will be collected on the same IT-platform as the web-based customized survey. All individual patient documentation is stored encoded and the same code is used in both the central database with CRFs and the web-based survey.

Biobank specimens and the patient associated clinical data will be stored for 30 years.

The management of intellectual property rights and the ownership of the data is discussed in detail in the contract documents.

11. SAFETY REPORTING

11.1 Ethical Committee

The investigator will inform the subjects and the reviewing accredited Ethical Committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited Ethical Committee, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

11.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to acetylsalicylic acid.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing patients' hospitalization
- results in persistent or significant disability or incapacity is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an Investigational Medicinal Product (IMP) used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SUSARs will be reported through the web portal of the FAGG and to the accredited Ethical Committee that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.
SUSARs that result in unexpected admissions, death, or are life threatening qualify for expedited reporting. The expedited reporting will occur no later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.
All SAEs, irrespective of relationship to the study treatment must be reported to the UZA oncology department by mail to aspirin@uza.be as soon as possible but no later than one working day from the time the local investigator has first knowledge of the SAE. UZA will inform the trial coordinator and the principal investigator. UZA will also inform the Medical Ethics Committee(s) and the Competent Authority as described in the previous section (see appendix 11).

NOTE: In this study, the following events are not considered an AE or SAE:

- Chemotherapy toxicity not resulting in admission
- Admission for diagnosis or treatment of recurrences. For recurrences, the CRF "new primary / recurrences" has to be filled in
- Death due to progression of disease
- Planned admissions. E.g. a knee operation (prosthesis for the knee) due to gonarthrosis. However, gonarthrosis is an AE

11.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Suspected unexpected serious side effects. This is the case in the following:

1. Serious event
2. Suspected is that the administered drug is related to the event
3. The side effect has not been written in existing product information e.g. Investigator's Brochure or summary of product characteristics (SPC).

The expedited reporting will occur not later than 7 days (in case life threatening) to 15 days (in case not life threatening)- after the investigator has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

11.2.2 Recording of adverse events

Relevant adverse events (i.e. AEs that may be related to the study medication) of any kind and any grade (e.g. bruises, gingival bleedings, epistaxis and thrombocytopenia), as well as all AEs grade 3 or more, reported spontaneously by the subject or observed by the investigator or his staff will be recorded on the AEs form of the CRF with the following information:

1. The severity grade according to the NCI-CTCAE version 4.0, published May 28, 2009 (appendix 7) (1=mild, 2=moderate, 3=severe, 4=life threatening)
2. Whether it constitutes a SAE

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the AE should be recorded on the AE CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changed in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome. Information about common side effects already known about the investigational drug can be found in the SPC.

11.2.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the central ethical committee of the UZA for distribution to all ethical advisory boards of participating hospitals.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation

11.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

11.4 Data Safety Monitoring Board (DSMB)

A DSMB will be established to evaluate the interim analyses on the safety data. This committee is independent of the conducted trial. The DSMB will be composed of three independent members, of whom at least one is a statistician. The members of the DSMB are independent and have no conflicts of interest with the conducted trial, principal investigator or sponsor of the study. Interim analyses are performed according to chapter 12.4. Accumulating data is reviewed, including updated figures on recruitment, data quality, primary outcome and safety data. The interim analysis will be performed deblinded by an independent statistician. The statistician will report to the independent DSMB. The DSMB will discuss the results of the interim-analysis and advice the steering committee. Discontinuation of the trial is advised by the DSMB according to the predefined stopping guidelines stated in paragraph 10.4.

Both the Dutch and Belgium safety data will be taken into account by the overall DSMB. See chapter 7.5.1 about the collaboration between LUMC and UZA.

11.5 Monitoring

Monitoring in Belgium will be done according to table 2 of the Netherlands Federation of University Medical Centres (NFU) guideline 'Kwaliteitsborging mensgebonden onderzoek 2.0' chapter 6. The ASPIRIN Trial is classified as a low-risk trial and therefore minimal monitoring is required (see appendix 10).

Objective of on-site monitoring:

To identify procedural errors in the execution of the research

Central monitoring:

- Detection of missing, late and inaccurate research

Source Data Verification:Monitoring will be performed according to the data monitoring plan.

- Randomisation form (F01) all items, including the
  - General information
  - Inclusion criteria
  - Exclusion criteria
  - Informed consent date
  - Specific questions
- Baseline form (F02)
  - Chemotherapy given according to stratification at randomisation
- Follow-up forms (F03)
  - Therapy compliance
  - Disease status
- Recurrence form (F04) (if applicable) all items, including the
  - Type of event
  - Locations
  - Investigations and results
  - Completeness/missed events
- End of study treatment form (F06) (if applicable)
  - Date of last study medication intake
  - Reason for end of study treatment
  - Study treatment deblinded
- Off study form (F07) (if applicable)
  - Last date in study
  - Reason off study
- Death form (F20) (if applicable)
  - Date of death
  - Cause of death
- Adverse Event forms (F30) (if applicable)
  - Completeness/missed AEs
- SAE forms (F40) (if applicable)
  - Completeness/missed SAEs

12. STATISTICAL ANALYSIS

12.1 Descriptive statistics

In both of the parallel trials, the number of patients will be described for acetylsalicylic acid and placebo. Rates and reasons for study discontinuation will be presented in contingency table(s). Patient characteristics at study entry will be summarised in frequency tables and descriptive statistics will be provided for patient and tumour variables.
The following information about the study treatment administration will be provided:

- The number of patients who have started on treatment, with details regarding the identification of the patients who should have started, and the reasons for the non-adherence to the protocol
- The number of patients who stopped the protocol treatment with the reasons for stopping treatment, complemented with a description of the cases who stopped for toxicity (detailing the patient identification and the type of toxicity)
- A summary of the duration of treatment. If all patients have finished treatment, the duration will be summarized using median and ranges of the actual treatment duration. If the treatment is still ongoing for some patients, the median treatment duration will be estimated using Kaplan-Meier curves
- Data in the web-based customized survey describe the patient reported different grades of toxicity based on the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and unravel, if any, difference in toxicity levels or frequencies between the 2 patient groups (with and without adjuvant chemotherapy)
- Data in the web-based customized survey describe therapy compliance and the individual patient reported outcome scores resulting from the questionnaires: QLQ-C30, modified ADL and IADL
- Data in the web-based customized survey describe the results on genetic analysis of the tissue sample. These data will be correlated with overall survival and disease-free survival with appropriate methods (Cox Proportional Hazard Model) to identify subpopulations with greater adjuvant benefit using acetylsalicylic acid

The “intention to treat population” will be used for analysis. This population will include the data of all patients randomised, regardless of whether patients received the acetylsalicylic acid or not or discontinued treatment. This population will be the primary population to evaluate survival. Besides this, a “per-protocol” analysis will be made where patients’ data will be analysed according to the study medication they actually used.

12.2 Univariate analysis

The two arms will be compared using a 2-sided non-stratified log-rank test at the 0.05 level of significance. Survival curves will be estimated using the Kaplan-Meier technique. Analysis will be performed for both parallel studies separately, so for patients who do receive chemotherapy and patients who did not receive chemotherapy. Univariate Cox proportional hazard models will be

used to estimate the Hazard Ratio and confidence interval for OS and DFS in the acetylsalicylic acid arm versus placebo. These analyses will be adjusted to the possible confounding factors.

12.3 Multivariate analysis

To adjust for potential confounders, multivariable Cox proportional hazards model will be used to estimate an adjusted HR and 95%CI for acetylsalicylic acid versus placebo in which we include all factors that were associated with survival (OS, DFS) in univariate analysis.

12.4 Interim analysis

- An interim analysis will be performed when half of the required events have been observed, in both arms 219/2 (=109)
- An alpha-spending function with an O'Brien-Fleming boundary will be used in order to be flexible with respect to the timing of the analysis
- A futility analysis will take place at the same time with two stopping rules:
  1. when>5% of patients experience serious side effects and
  2. when results indicate that it is unlikely that results at the scheduled end of the trial will demonstrate a significant effect (differences between acetylsalicylic acid and control group are that small that any prospect of a positive result with the planned sample size is very unlikely). Probability and conditional power will be calculated; if this probability is too small to meet the pre-specified criteria, we will stop the trial for futility
- The final analysis of the trial will be done when the required number of events has been recorded for all patients evaluated by the Study Coordinator

13. ETHICAL CONSIDERATIONS

13.1 Regulation statement

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol will be approved by the local, regional or national ethics committees.

13.2 Recruitment and consent

A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patients date or birth will be reported on the case report forms as well.
All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.
It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomised. This must be done in accordance with the national and local regulatory requirements.
A time window of 3 weeks is used between the signing of the informed consent and the day of randomization. The informed consent must be kept as hardcopy and preferably also digitally in the electronic patient file.
The informed consent procedure must conform to the ICH guidelines of Good Clinical Practice. This implies that the written information must be personally signed and dated by the patient.

13.3 Objection by minors or incapacitated subjects

Patients that are not competent to make decisions on their own are not eligible for this trial.

13.4 Benefits and risks assessment, group relatedness

The potential of the adjuvant use of acetylsalicylic acid is enormous. It involves a common, very cheap drug, with a well-known safety and side effect profile utilised in a conventional (cardiovascular) and non-conventional (adenocarcinoma, COX-2 inhibition) manner. In addition acetylsalicylic acid is not feared by patients in the same way that conventional chemotherapy is.

13.5 Compensation for injury

The sponsor has a liability insurance provided by AMMA (1887617) which will be annually renewed for the amount of 12.395.000 EUR.

14. DATA COLLECTION AND REPORTING DOCUMENTS

14.1 Guidelines completion of Case Report Forms (CRFs)

On the paper CRFs some fields are obligatory, and other fields are optional. If obligatory fields of a CRF-form are left open, this will be considered as a protocol deviation. The reason why an obligatory or optional field is left open has to be specified on the CRF-form. The person completing the CRF-form can therefore use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed. This information must be based on the medical record of the patient.
Some CRF-forms contain specific instructions to indicate if an additional CRF-form needs to be completed. For example, when a change in chronical concomitant medication is reported in a Follow-up Form, a Concomitant Medication Form (CRF F05) needs to be completed. When the additional CRF is not filled in when indicated, this is considered as a protocol deviation.
The obligatory and optional fields of the different CRF-forms are described in Appendix 9 (Guidelines for monitoring).
Investigators and/or authorized staff members should read and apply the guidelines carefully.

14.2 Amendments

Amendments are changes made to the research protocol after a favourable opinion by the accredited Ethical Committee has been given. All amendments will be notified to the Ethical Committee that gave an approval. Also amendments will be synchronized with the protocol of the Dutch ASPIRIN trial.
A 'substantial amendment' is defined as an amendment to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial

All substantial amendments will be submitted to the Ethical Committee for approval, and to the competent authority for notification.
Non-substantial amendments will be notified to the accredited Ethical Committee and the competent authority, and will be recorded and filed by the sponsor.

14.3 Annual progress report

The coordinating investigator will submit a summary of the progress of the trial to the accredited Ethical Committee once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

14.4 End of study report

The sponsor will notify the accredited Ethical Committee and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.
In case the study is ended prematurely, the sponsor will notify the accredited Ethical Committee and the competent authority within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethical Committee and the competent authority.

14.5 Public disclosure and publication policy

The final publication of the trial results will be written by the Study Chairman on the basis of the final analysis performed at the Datacenter Department of Surgery LUMC. A draft manuscript will be submitted by the study coordinator to the Datacenter for review no later than six months after receiving the Datacenter Report. After revision by the Datacenter and other co-authors the manuscript will be sent to a major scientific journal. Authors of the manuscript will include at least the coordinating investigator of Belgium, all Study Coordinators, the Project Manager and the members of the Datacenter team who have contributed to the trial. Due to the high number of participating centers only Local Investigators from centers both in Belgium and the Netherlands who have entered the top 8 of included patients qualify for co- authorship. The other Local Investigators qualify for acknowledgements. All publications, abstracts or presentations including data from the present trial will be submitted for review to the Datacenter prior to submission.
All manuscripts will include an appropriate acknowledgement section, mentioning all investigators who have contributed to the trial, as well as supporting bodies. The Group Chairman, the Study Coordinators and the Datacenter must approve all publications, abstracts and presentations based on patients included in this study. This is applicable to any individual patient registered/randomised in the trial, or any subgroup of the trial patients.

15. FINANCES

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17. APPENDICES

APPENDIX 1: EORTC QLQ-C30 (version 5)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 2: Modified ADL and IADL

KATZ ADL
Dit is een lijst met bezigheden, die te maken hebben met uw functioneren in het dagelijks leven. We willen u verzoeken de vragen in te vullen voor de situatie zoals deze op dit moment is.

Naam patiënt:
Datum:

Kruis aan wat van toepassing is.
Bij twijfel altijd ja in vullen!

ADL	DATUM:
1. Heeft hulp nodig bij baden en douchen	O nee O ja
2. Heeft hulp nodig bij het aankleden	O nee O ja
3. Heeft hulp nodig bij kammen van de haren of scheren	O nee O ja
4. Heeft hulp nodig bij het naar het toilet gaan	O nee O ja
5. Maakt gebruik van incontinentiemateriaal	O nee O ja
6. Heeft hulp nodig bij opstaan uit stoel	O nee O ja
7. Heeft hulp nodig bij het lopen	O nee O ja
8. Heeft hulp nodig bij het eten	O nee O ja
SUBTOTAAL ADL	*/8*
IADL	
1. Heeft hulp nodig bij het gebruiken van de telefoon	O nee O ja
2. Heeft hulp nodig bij reizen (dagelijks vervoer)	O nee O ja
3. Heeft hulp nodig bij het boodschappen doen	O nee O ja
4. Heeft hulp nodig bij het bereiden van een maaltijd	O nee O ja
5. Heeft hulp nodig bij huishoudelijk werk	O nee O ja
6. Heeft hulp nodig bij het innemen van medicijnen	O nee O ja
7. Heeft hulp nodig bij het omgaan met geld	O nee O ja
SUBTOTAAL IADL	*/7*
(gemodificeerd, Weinberger et al. JAGS 1992)	
Ja = 1 punt; nee = 0 punt	
Totaal aantal ja = totaal score op KATZ = (svp optellen en invullen)	*/15*

APPENDIX 3: PRO-CTCAE items

AE	Ernst NL	Sévérité FR
Vermoeidheid	Geen vermoeidheid	Pas de fatigue
Fatique	Vermoeidheid die overgaat door te rusten	Fatigue qui s'améliore grâce à du repos
	Gaat niet over door te rusten en stoort de dagdagelijkse taken (bv. koken, winkelen)	Ne passe pas grâce a du repos et perturbe les activités quotidiennes (ex. cuisiner, faire les courses)
	Gaat niet over door te rusten en stoort de zelfzorg (wassen, eten, etc.)	Ne passe pas grâce à du repos et perturbe la prise en charge personnelle (se laver, manger, etc)
Braken, misselijkheid	Afwezig	Absent
Vomissements/nausées	Weinig	Peu
	Matig	Modéré
	Ernstig	Grave
Huiduitslag	Afwezig	Absent
Réaction de peau	Minder dan 50% zonder pijn of jeuk	Moins que 50% de la peau et sans douleur ou démangeaisons
	Minder dan 50% met pijn of jeuk	Moins que 50% de la peau mais avec douleur ou démangeaisons
	Meer dan 50% (met of zonder symptomen)	Plus que 50% de la peau (avec ou sans symptomes)
Frequentie stoelgang	1	1
Fréquence de selles	2	2
	3	3
	4	4
	5	5
	6	6
	7	7
	8	8
	9	9
	9+	9+
Ontsteking in de mond	Geen klachten	Pas de plainte
Infection buccale	Lichte pijn maar er is geen interventie nodig	Légère douleur qui ne nécessite pas d'intervention
	Matige pijn, stoort niet tijdens het eten maar een aangepast dieet is aanbevolen	Douleur modérée, qui ne dérange pas pendant les repas mais qui requiert un régime adapté
	Ernstige pijn, stoort tijdens het eten	Douleur modérée, qui dérange fortement pendant la prise des repas
Huidaandoening	Ja	Oui
Lésion cutanée	Nee	Non
Haarverlies	Minder dan 50% van het haar verloren	La perte des cheveux est moins que 50%

Perte des cheveux	50% of meer van het haar verloren	La perte des cheveux est plus que 50%
Hospitalisatie	Gehospitaliseerd in behandelend ziekenhuis	Hospitalisé à l'hôpital habituel
Hospitalization	Gehospitaliseerd in ander ziekenhuis	Hospitalisé à un autre hôpital
Verminderde eetlust	Geen verminderde eetlust	Pas de perte d'appétit
	Mijn eetlust is minder, maar eetgewoonten worden niet aangepast	Je perds l'appétit mais mes habitudes alimentaires ne sont pas modifiés
	Ik kan minder eten maar verlies geen gewicht	Je sais moins manger mais je ne perds pas de poids
	Ik kan niet (voldoende) eten en verlies bijgevolg gewicht	Je sais moins manger et je perds du poids
Verstopping	Geen	Pas de constipation
	Stoelgang met af en toe hulpmiddel (fruit, laxeermiddel,…)	Symptômes occasionnels ou intermittents de constipation ; recours occasionnels à des laxatifs, adaptations diététiques (fruits,…)ou lavements
	Stoelgang met dagelijkse nood aan hulpmiddel (fruit, laxeermiddel,..)	Symptômes persistants avec utilisation journalière de laxatifs ou de lavements
	Ik heb zo veel last van verstopping dat het mijn dagelijkse activiteiten belemmert en hulpmiddelen niet helpen	Constipation opiniâtre avec nécessité d'évacuation manuelle ou interférant avec les activités élémentaires de la vie quotidienne
Tintelingen vingers/tenen Picotements main/pied	Geen	Pas de picotements ou fourmillements
	Ik heb hier last van, maar verstoort mijn functioneren niet	Je souffre de picotements ou fourmillements mais cela ne perturbe pas mes activités quotidiennes
	Ik heb hier last van en sommige van mijn dagelijkse activiteiten lukken daardoor moeilijker	Symptômes modérés ; interférant avec les activités de la vie quotidienne

	Ik heb hier last van en sommige van mijn dagelijkse activiteiten lukken daardoor niet	Symptômes sévères ; empêchant les activités élémentaires de la vie quotidienne
Regelmatige neusbloedingen	Neen	Non
	Ja	Oui
Kortademigheid	Afwezig	Absent
	Kortademig bij beperkte inspanning	Essouflement à l'effort modéré (monter les esclaiers)
	Kortademig bij minimale inspanning	Essouflement au moindre effort
	Kortademig bij rust	Essouflement même au repos
Hand- en voet huidreactie	Geen klachten	Pas de plainte
	Minimale huidveranderingen zonder pijn (bv. roodheid)	Anomalie cutanée minimale, sans douleur (ex. rougeur)
	Huidveranderingen met pijn (bv.blaren, klovenbloeden), stoort de dagdagelijkse taken (bv.koken, winkelen)	Anomalie cutanée avec douleur (ex. cloques, crevasses), perturbe les activités quotidiennes (ex. cuisiner)
	Ernstige huidveranderingen met pijn (bv. blaren, kloven, bloeden), stoort de zelfzorg (bv. wassen, eten)	Anomalie cutanée grave et douleur (ex. cloques, saignements), perturbe prise en charge personnelle (ex. se laver)
Dorstgevoel & frequent plassen	Neen	Non
	Ja	Oui
Slapeloosheid	Afwezig	Absent
	Ik val moeilijk in slaap, wordt vaak wakker 's nachts	Je m'endors difficilement, je me réveille souvent la nuit
	Ik kan nog amper slapen	Je n'arrive pas à dormir

APPENDIX 4: G8

To be completed by: Clinician or trained coder.

Geriatric Assessment Screening tool			
	Items	Possible answers	Score
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	**0**: severe reduction in food intake **1**: moderate reduction in food intake **2**: normal food intake	.....
B	Weight loss during the last 3 months?	**0**: weight loss >3kg **1**: does not know **2**: weight loss between 1 and 3 kg **3**: no weight loss	.....
C	Mobility	**0**: bed or chair bound **1**: able to get out of bed/chair but does not go out **2**: goes out	.....
E	Neuropsychological problems	**0**: severe dementia or depression **1**: mild dementia or depression **2**: no psychological problems	.....
F	Body Mass Index (weight in kg/height in m2)	**0**: BMI less than 19 **1**: BMI 19 to less than 21 **2**: BMI 21 to less than 23 **3**: BMI 23 or greater	.....
H	Takes more than 3 medications per day	**0**: yes **1**: no	.....
P	In comparison with other people of the same age, how does the patient consider his/her health status?	**0**: not as good **0,5**: does not know **1**: as good **2**: better	.....
	Age	**0**: >85 **1**: 80-85 **2**: <80	.....
	Total score (0-17)		

Score >14: Absence of geriatric risk profile

Score ≤14: Presence of geriatric risk profile

APPENDIX 5: ACE-27

To be completed by: Clinician or trained coder.

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Cardiovascular System			
Myocardial Infarct	☐ MI ≤ 6 months	☐ MI > 6 months ago	☐ MI by ECG only, age undetermined
Angina / Coronary Artery Disease	☐ Unstable angina	☐ Chronic exertional angina ☐ Recent (≤ 6 months) Coronary Artery Bypass Graft (CABG) or Percutaneous Transluminal Coronary Angioplasty (PTCA) ☐ Recent (≤ 6 months) coronary stent	☐ ECG or stress test evidence or catheterization evidence of coronary disease without symptoms ☐ Angina pectoris not requiring hospitalization ☐ CABG or PTCA (>6 mos.) ☐ Coronary stent (>6 mos.)
Congestive Heart Failure (CHF)	☐ Hospitalized for CHF within past 6 months ☐ Ejection fraction < 20%	☐ Hospitalized for CHF >6 months prior ☐ CHF with dyspnea which limits activities	☐ CHF with dyspnea which has responded to treatment ☐ Exertional dyspnea ☐ Paroxysmal Nocturnal Dyspnea (PND)
Arrhythmias	☐ Ventricular arrhythmia ≤ 6 months	☐ Ventricular arrhythmia > 6 months ☐ Chronic atrial fibrillation or flutter ☐ Pacemaker	☐ Sick Sinus Syndrome ☐ Supraventricular tachycardia
Hypertension	☐ DBP≥130 mm Hg ☐ Severe malignant papilledema or other eye changes ☐ Encephalopathy	☐ DBP 115-129 mm Hg ☐ DBP 90-114 mm Hg while taking antihypertensive medications ☐ Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	☐ DBP 90-114 mm Hg while not taking antihypertensive medications ☐ DBP <90 mm Hg while taking antihypertensive medications ☐ Hypertension, not otherwise specified
Venous Disease	☐ Recent PE (≤ 6 mos.) ☐ Use of venous filter for PE's	☐ DVT controlled with Coumadin or heparin ☐ Old PE > 6 months	☐ Old DVT no longer treated with Coumadin or Heparin
Peripheral Arterial Disease	☐ Bypass or amputation for gangrene or arterial insufficiency < 6 months ago ☐ Untreated thoracic or abdominal aneurysm (≥6 cm)	☐ Bypass or amputation for gangrene or arterial insufficiency > 6 months ago ☐ Chronic insufficiency	☐ Intermittent claudication ☐ Untreated thoracic or abdominal aneurysm (< 6 cm) ☐ s/p abdominal or thoracic aortic aneurysm repair
Respiratory System			
	☐ Marked pulmonary insufficiency ☐ Restrictive Lung Disease or COPD with dyspnea at rest despite treatment ☐ Chronic supplemental O_2 ☐ CO_2 retention (pCO_2 > 50 torr) ☐ Baseline pO_2 < 50 torr ☐ FEV1 (< 50%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which limits activities ☐ FEV1 (51%-65%)	☐ Restrictive Lung Disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea which has responded to treatment ☐ FEV1 (66%-80%)
Gastrointestinal System			
Hepatic	☐ Portal hypertension and/or esophageal bleeding ≤ 6 mos. (Encephalopathy, Ascites, Jaundice with Total Bilirubin > 2)	☐ Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms "compensated hepatic failure"	☐ Chronic hepatitis or cirrhosis without portal hypertension ☐ Acute hepatitis without cirrhosis ☐ Chronic liver disease manifested on biopsy or persistently elevated bilirubin (>3 mg/dl)
Stomach / Intestine	☐ Recent ulcers(≤ 6 months ago) requiring blood transfusion	☐ Ulcers requiring surgery or transfusion > 6 months ago	☐ Diagnosis of ulcers treated with meds ☐ Chronic malabsorption syndrome ☐ Inflammatory bowel disease (IBD) on meds or h/o with complications and/or surgery
Pancreas	☐ Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	☐ Uncomplicated acute pancreatitis ☐ Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or GI bleeding)	☐ Chronic pancreatitis w/o complications

Cogent comorbid ailment	Grade 3 Severe Decompensation	Grade 2 Moderate Decompensation	Grade 1 Mild Decompensation
Renal System			
End-stage renal disease	☐ Creatinine > 3 mg% with multi-organ failure, shock, or sepsis ☐ Acute dialysis	☐ Chronic Renal Insufficiency with creatinine >3 mg% ☐ Chronic dialysis	☐ Chronic Renal Insufficiency with creatinine 2-3 mg%.
Endocrine System	**(Code the comorbid ailments with the (*) in both the Endocrine system and other organ systems if applicable)**		
Diabetes Mellitus	☐ Hospitalization ≤ 6 months for DKA ☐ Diabetes causing end-organ failure ☐ retinopathy ☐ neuropathy ☐ nephropathy* ☐ coronary disease* ☐ peripheral arterial disease*	☐ IDDM without complications ☐ Poorly controlled AODM with oral agents	☐ AODM controlled by oral agents only
Neurological System			
Stroke	☐ Acute stroke with significant neurologic deficit	☐ Old stroke with neurologic residual	☐ Stroke with no residual ☐ Past or recent TIA
Dementia	☐ Severe dementia requiring full support for activities of daily living	☐ Moderate dementia (not completely self-sufficient, needs supervising)	☐ Mild dementia (can take care of self)
Paralysis	☐ Paraplegia or hemiplegia requiring full support for activities of daily living	☐ Paraplegia or hemiplegia requiring wheelchair, able to do some self care	☐ Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but able to do some self care	☐ MS, Parkinson's, Myasthenia Gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	☐ Recent suicidal attempt ☐ Active schizophrenia	☐ Depression or bipolar disorder uncontrolled ☐ Schizophrenia controlled w/ meds	☐ Depression or bipolar disorder controlled w/ medication
Rheumatologic	**(Incl. Rheumatoid Arthritis, Systemic Lupus, Mixed Connective Tissue Disorder, Polymyositis, Rheumatic Polymyositis)**		
	☐ Connective Tissue Disorder with secondary end-organ failure (renal, cardiac, CNS)	☐ Connective Tissue Disorder on steroids or immunosuppressant medications	☐ Connective Tissue Disorder on NSAIDS or no treatment
Immunological System	**(AIDS should not be considered a comorbidity for Kaposi's Sarcoma or Non-Hodgkin's Lymphoma)**		
AIDS	☐ Fulminant AIDS w/KS, MAI, PCP (AIDS defining illness)	☐ HIV+ with h/o defining illness. $CD4^+ < 200/\mu L$	☐ Asymptomatic HIV+ patient. ☐ HIV^+ w/o h/o AIDS defining illness. $CD4^+ > 200/\mu L$
Malignancy	**(Excluding Cutaneous Basal Cell Ca., Cutaneous SCCA, Carcinoma in-situ, and Intraepithelial Neoplasm)**		
Solid Tumor including melanoma	☐ Uncontrolled cancer ☐ Newly diagnosed but not yet treated ☐ Metastatic solid tumor	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated within the last 5 years	☐ Any controlled solid tumor without documented metastases, but initially diagnosed and treated > 5 years ago
Leukemia and Myeloma	☐ Relapse ☐ Disease out of control	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o leukemia or myeloma with last Rx > 1 yr prior
Lymphoma	☐ Relapse	☐ 1st remission or new dx <1yr ☐ Chronic suppressive therapy	☐ H/o lymphoma w/ last Rx >1 yr prior
Substance Abuse	**(Must be accompanied by social, behavioral, or medical complications)**		
Alcohol	☐ Delirium tremens	☐ Active alcohol abuse with social, behavioral, or medical complications	☐ H/o alcohol abuse but not presently drinking
Illicit Drugs	☐ Acute Withdrawal Syndrome	☐ Active substance abuse with social, behavioral, or medical complications	☐ H/o substance abuse but not presently using
Body Weight			
Obesity		☐ Morbid (i.e., BMI ≥ 38)	

OVERALL COMORBIDITY SCORE (Circle one.) **0** None **1** Mild **2** Moderate **3** Severe **9** Unknown

APPENDIX 6: Social Situation

To be completed by: Clinician or trained coder.

Question to the patient:

Which of the following statements best describes where you live?

•At home by myself

•At home with someone

•In institutional care (for example residential home or nursing home)

APPENDIX 7: CTCAE v4.0

The grading of adverse events and/or adverse drug reactions will be reported according to the NCI Common Terminology Criteria for Adverse Events, **CTCAE version 4.0**,

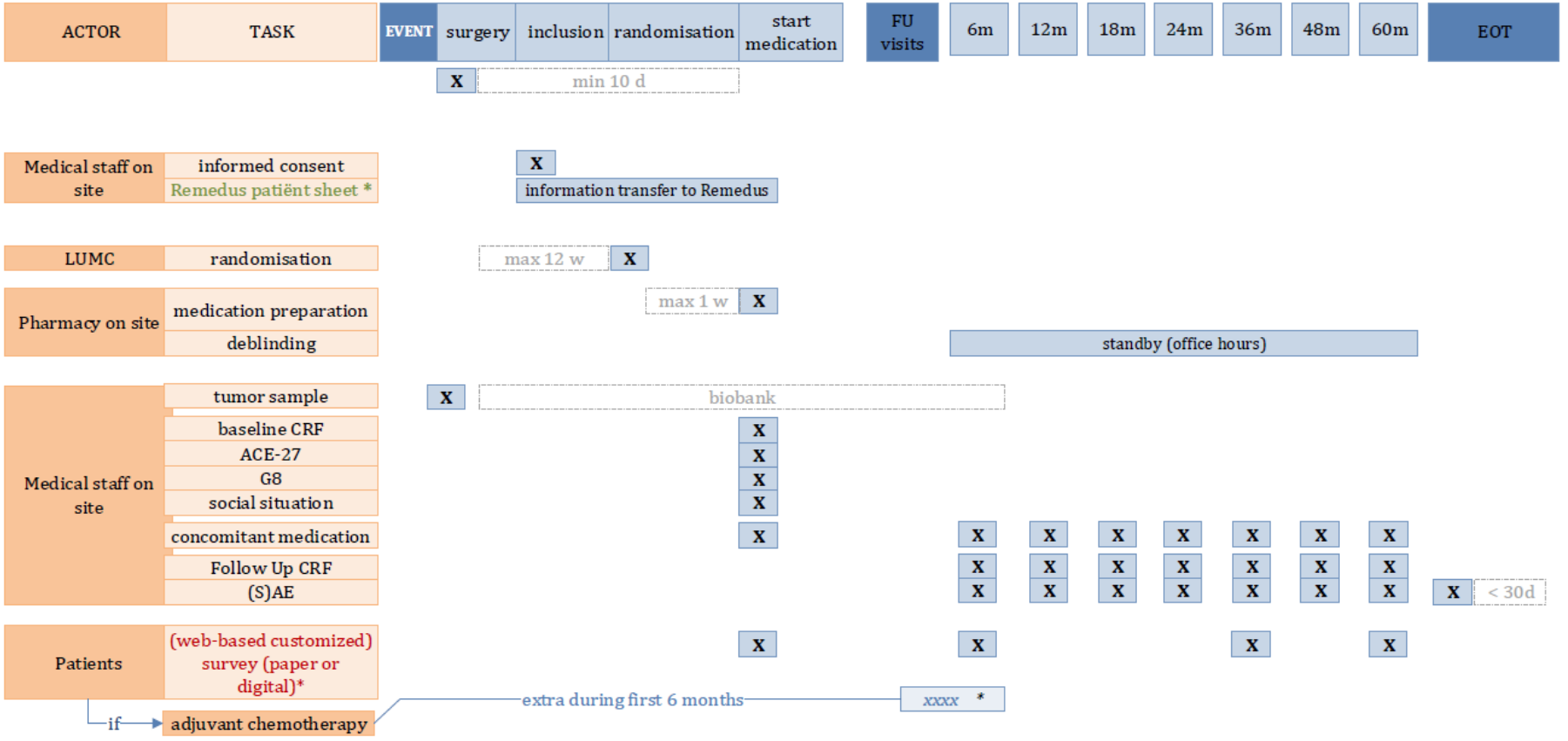
The complete document can be reviewed and downloaded from the following

internet site:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

ASPIRIN PROTOCOL SCHEME

V2.0 dd.18/12/2018



List of abbreviations
LUMC: Leidens Universitair Medisch Centrum
EOT: End Of Trial
CRF: Clinical Research Form
ACE: Adult Comorbidity Evaluation
G8: Geriatric Assessment Screening tool
(S)AE: (Serious) Adverse Event

**(Web-based customized) survey contains:*
QLQC30: Quality of life Questionnaire
ADL: Activities of Daily Living
IADL: Instrumental Activities of Daily Living
*xxxx * PRO-CTCAE: Patient Reported Outcome-Common Terminology Criteria for Adverse Events*
** Therapy Compliance information*

**Remedus patient sheet contains:*
Identification: Center ID, Subject ID, Date of birth
Information: Start date medication, adjuvant chemo (y/n)
Communication: E-mail address of all patients, full address and phone n° if adjuvant chemo

APPENDIX 9: Guidelines for monitoring

9.1. NFU guideline for monitoring

The monitoring will be done according to table 2 of the NFU guideline 'Kwaliteitsborging mensgebonden onderzoek' version 2.0, chapter 6. The complete guideline can be found at the NFU website:

http://www.nfu.nl/img/pdf/NFU-12.6053_Kwaliteitsborging_mensgebonden_onderzoek_2.0.pdf

Minimal monitoring is required because the ASPIRIN Trial is classified as a low-risk trial. In Dutch: 'Verwaarloosbaar risico = Minimale monitoring'.

9.2. Monitoring guidelines for CRF completion

Randomisation Form (CRF F01):

Obligatory fields	**Optional fields**
- Center Id - Subject Id - Date of Birth: day, month and year - Name and function of the physician - Center name - Inclusion criteria: all answers must be 'yes' otherwise patient is not eligible - Exclusion criteria: all answers must be 'no' otherwise patient is not eligible - Date of written informed consent - Date of surgery - Adjuvant chemotherapy (no/yes) - Stage - Gender - Date of randomisation - Signature and name investigator - Date signed by investigator	- Notes
The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Notes:

- The signature and name of the datacenter, as well as the date signed by the datacenter are automatically completed by ProMISe when a randomisation has been performed.
- The physician who included the patient (cfr. page 1 'General Information') must also sign the randomisation form.

Baseline Form (CRF F02):

Obligatory fields	Optional fields

- Center Id
- Subject Id
- Date of Birth: month and year
- CEA at baseline (pre-operative) and date of CEA at baseline
- Adult comorbidity evaluation (ACE -27): all criteria must be filled in.
- G8 geriatric assessment screening tool & social status: all criteria must be filled in.
- Chronical use of concomitant medication (yes/no). If concomitant medication was used, the name has to be specified.
- Adjuvant chemotherapy started (no/yes)
  o If the answer is 'no': the reason chemotherapy was not started has to be filled in.
  o If the answer is 'yes': date of first dose, drugs and dose, number of courses and chemotherapy completed (no/yes/not yet completed) has to be filled in. If chemotherapy is not completed, the reason has to be specified. If chemotherapy is completed, the date of last dose has to be specified.
- Signature and name investigator
- Date signed
	- Dose of concomitant medication if mentioned in the medical record
	- Notes

The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Note: the Carcinoembryonic antigen (CEA) value has to be reported in µg/L.

Follow-up Forms (CRF F03):

Obligatory fields	Optional fields
- Center Id - Subject Id - Date of Birth: month and year - Date of visit - Randomized therapy started (no/yes). If yes: date of start randomized therapy - Randomized therapy stopped (yes/no) - Pattern of compliance - CEA at X months. Provide date if done - US liver/abdomen. Provide date if done - CT liver/abdomen. Provide date if done - Other investigations: provide specification and date if done - Locoregional recurrence - Distant metastases - New primary tumour - Toxicity/Adverse Events (no/yes) - Serious Adverse Event (no/yes) - Changes Chronical Concomitant Medication (no/yes) - Signature and name investigator - Date signed	- Notes
The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Notes:

- This information is applicable for all follow-up forms used in this study.
- The Carcinoembryonic antigen (CEA) value has to be reported in µg/L.
- If applicable, complete an additional CRF-form according to the instructions on this CRF-form.

Recurrence/New Primary Form (CRF F04):

Obligatory fields	Optional fields
- Center Id - Subject Id - Date of Birth: month and year - Locoregional recurrence. If yes: provide date of diagnosis - Distant metastases. If yes: provide date of diagnosis - New primary tumour. If yes: provide date of diagnosis - Location(s): see instructions below (*) - Cytology: provide date if done - Histology: provide date if done - Bone Scintigraphy (bone scan): provide date if done - Chest X ray: provide date if done - CT chest: provide date if done - US liver/abdomen: provide date if done - CT liver/abdomen: provide date if done - MRI scan: provide date if done - PET scan: provide date if done - CEA: provide value and date if done - Other investigations and results: provide date if done - Signature and name investigator - Date signed	- Notes
The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

(*) Instructions for locations:

- Location of locoregional recurrence (refers to recurrence of colon cancer)
  - Original tumour location
  - At anastomosis
  - Regional lymph node(s)
  - Skin local area
  - Other
  - Unknown
- Location of distant metastases (use abbreviation please)
  - Pulmonary → PUL
  - Osseous → OSS
  - Hepatic → HEP
  - Brain → BRA
  - Distant lymph nodes → LYM
  - Bone marrow → MAR
  - Pleura → PLE
  - Peritoneum → PER
  - Adrenals → ADR

        - Skin → SKI
        - Other → OTH
        - Unknown
    - Location of new primary tumour
        - Bladder
        - Breast
        - Colon
        - Endometrium
        - Lung
        - Prostate
        - Other
        - Unknown

Notes:

- A new CRF-form recurrence/new primary needs to be filled in for each new recurrence or new primary tumour.
- The Carcinoembryonic antigen (CEA) value has to be reported in µg/L.

Concomitant Medication Form (CRF F05):

Obligatory fields	**Optional fields**

- Center Id
- Subject Id
- Date of Birth: month and year
- Chronical Medication Stopped (no/yes)
  o If chronical concomitant medication is stopped: provide date of stop and name of stopped chronical concomitant medication
  o If chronical concomitant medication is started: provide date of start and name of started chronical concomitant medication
- Signature and name investigator
- Date signed
	- If chronical concomitant medication is stopped: provide dose and reason of stop(ped) chronical concomitant medication
	- If chronical concomitant medication is started: provide dose and reason of start(ed) chronical concomitant medication
	- Notes

The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Notes:

- Changes in type of concomitant medication as well as dosage need to be registered in the Concomitant Medication Form (CRF F05).
- **If the concomitant medication is related to an adverse event grade 1/2 and not considered to be relevant, please mention this AE + grade in the Notes field of the Concomitant Medication Form (CRF F05).**

End of Study Treatment Form (CRF F06):

Obligatory fields	Optional fields
- Center Id - Subject Id - Date of Birth: month and year - Date of last study medication intake - Reason for end of study treatment - Study treatment deblinded (no/yes) - Signature and name investigator - Date signed	- Notes
The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Notes:

- If applicable, complete an additional CRF-form according to the instructions on this CRF-form.
- An End of Study Treatment Form needs to be completed when a patient stops/must stop his/her study medication for any reason, but there is no withdrawal of Informed Consent. The scheduled study visits continue, but no questionnaires should be completed anymore.

Off Study Form (CRF F07):

Obligatory fields	Optional fields
- Center Id - Subject Id - Date of Birth: month and year - Last date in study - Reason off study - Signature and name investigator - Date signed	- Notes
The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Notes:

- If applicable, complete an additional CRF-form according to the instructions on this CRF-form.
- An Off Study Form needs to be completed in case of end of study treatment and withdrawal of Informed Consent. The data collection stops i.e. no questionnaires should be completed anymore, and no more study visits will be organized.

Death Form (CRF F20):

Obligatory fields	Optional fields
- Center Id - Subject Id - Date of Birth: month and year - Date of death - Autopsy (no/yes). If an autopsy is performed, the autopsy report must be sent to the central coordination team (aspirin@uza.be) - Cause of death. If 'second primary malignancy' or 'other' is applicable, a specification needs to be filled in - Signature and name investigator - Date signed	- Notes
The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Adverse Event Form (CRF F30):

Obligatory fields	Optional fields
- Center Id - Subject Id - Date of Birth: month and year - Description of AE - Date of visit - Date of onset AE - Serious Adverse Event (no/yes) - Grade AE - Relation AE to study medication - Action with study medication - Treatment of the AE - Outcome AE - Date resolved AE if date is known in the medical record - Signature and name investigator - Date signed	- Date resolved AE if date is unknown in the medical record
The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Notes:

- The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 needs to be used for Adverse Event reporting. A grading (severity) scale is provided herein for each Adverse Event term. Grade 3-5 adverse events should always be reported. In addition, relevant (possibly related) adverse events grade 1-2 (e.g. bruises, gingival bleedings, epistaxis and thrombocytopenia) should also be reported. In this study chemotherapy toxicity is not considered an adverse event (cfr. Protocol Chapter 11.2).
- If applicable, complete an additional CRF-form according to the instructions on this CRF-form.

Serious Adverse Event Form (CRF F40):

Obligatory fields	Optional fields

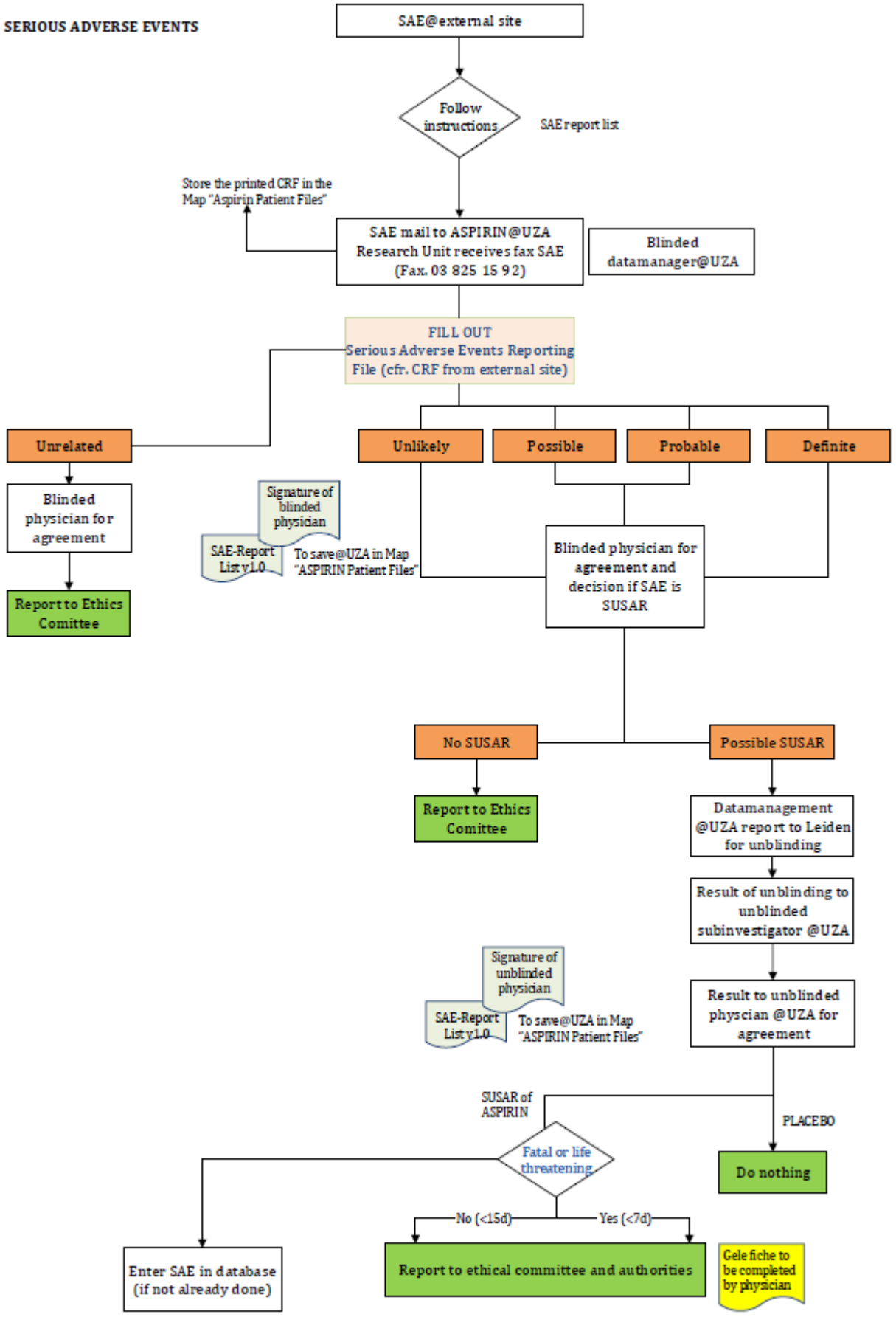
- Center Id
- Subject Id
- Date of Birth: month and year
- Report type
- Country
- Age (years)
- Sex
- Date of onset SAE
- Onset period of SAE
- Description SAE in a single term
- Intensity SAE according to CTCAE version 4.03
- Category of SAE. If the category 'patient died' is applicable, the date of death and cause of death has to be completed
- Outcome SAE. If the patient recovered, the date of recovery has to be completed
- First date of administration of Aspirin or Placebo
- Last date of administration of Aspirin or Placebo
  o In case of EOT: report date of EOT
  o In case of temporarily stop: report date of last administration
- Causality
- Did reaction abate after stopping study medication?
- Did reaction reappear after reintroduction study medication?
- Action taken?
- Concomitant medication (yes/no). If concomitant medication was used, the name has to be specified
- Relevant laboratory values
- Date of initial report or N.A.
- Date of final report or N.A.
- Contact details of the person who filled out this form and e-mail address
- Signature and name investigator
- Date signed
	- Dose of concomitant medication if applicable
	- Relevant medical history
	- Notes
	- If applicable, report date of reintroduction study medication after temporarily stop in Notes field of SAE form

The person completing the CRF-form can use the abbreviations 'UK' (unknown) or 'ND' (not done) if applicable. 'UK' must be used when it is not known if a value has been measured or a test has been performed. 'ND' must be used when it is certain that a value has not been measured or a test has not been performed.	

Questionnaires

The questionnaires on T0, T6, T36 and T60 are considered as obligatory. When a questionnaire is not completed or is missing, this is regarded as a protocol deviation. Please provide the reason why the questionnaire has not been completed or is missing.

APPENDIX 10: Safety Manual



SERIOUS ADVERSE EVENTS