Service de Gynécologie
30 Bd de la Cluse
1211 Genève
Tél : 022 372 68 16

"Fast track" surgery on patient undergoing minimally invasive gynaecologic procedure: a randomized clinical trial

SEPTEMBER 29TH 2015
VERSION 2.0

MAIN INVESTIGATOR
LAMBAT EMERY SHAHZIA

CO-INVESTIGATORS
PETIGNAT PATRICK
BROSSARD PHILIPPE
DALLENBACH PATRICK
DUBUISSON JEAN
WENGER JEAN-MARIE
BOULVAIN MICHEL
BRIET VIRGINIE

RESEARCH NURSES
ROYANNEZ DREVARD ISABELLE
GUILLOT CECILE

"Fast track" surgery on patient undergoing minimally invasive gynaecologic procedure: a randomized clinical trial

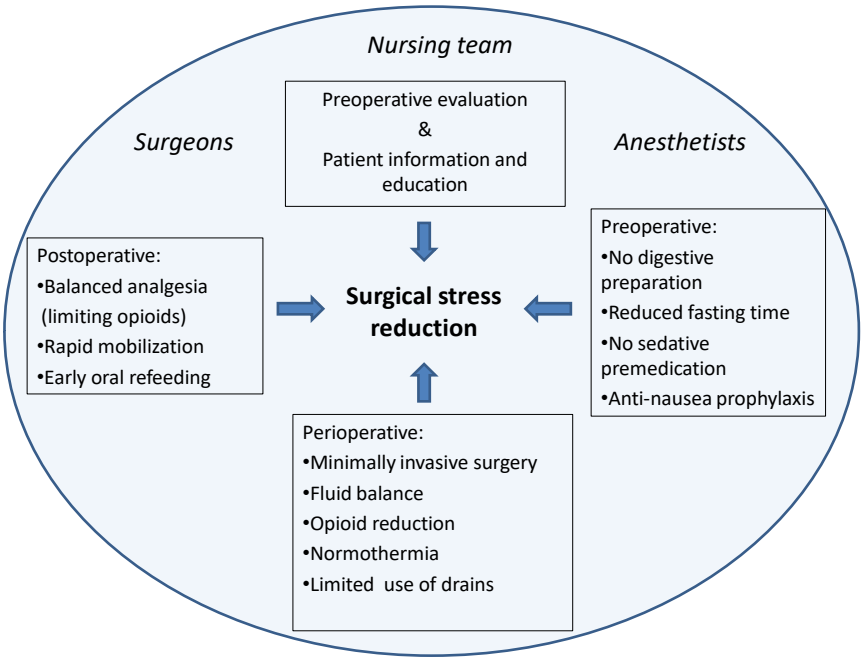
Introduction:

The concept of "*enhanced recovery*" was developed by American cardiologists in the 1950s to improve patient rehabilitation after a myocardial infarction. In 1995, this concept was extended to colonic surgery by Kehlet et al. who developed a perioperative multimodal strategy currently known as *'Fast track' (FT)*, or " *Enhanced recovery after surgery* ' (ERAS).[1] This innovative concept suggests including the combination of minimally invasive surgery, analgesia optimization, early oral refeeding and rapid mobilization of patients which reduces pain and organic dysfunction induced by surgical stress. This concept, increasingly applied worldwide in colorectal surgery, has also shown efficiency by reducing hospitalization lenght.[2.3] Gynaecological surgery, similar to colonic surgery in many ways, has very little explored this concept.

The concept of "*Fast track"* or "*Enhanced recovery after surgery"*:

FT is a global perioperative approach aiming to optimize patient care by early rehabilitation. The objectives are to reduce post-operative pain and organic dysfunction induced by surgical stress. This strategy facilitates recovery and comfort of patients while decreasing morbidity, hospitalization length and costs.[3-5] This multimodal approach requires a close and well codified multidisciplinary collaboration in between surgeons, anaesthetists and the nursing team. The key elements of the program include preoperative patient information and education, lack of digestive preparation, perioperative water balance, analgesia optimization, early oral refeeding and rapid mobilization of patients.[5-7] These elements can be classified into four subgroups in terms of overall support: 1) patient information and education, 2) preoperative, 3) perioperative and 4) postoperative (Figure 1).

Figure 1



The patient, at the centre of this concept, is a major actor. Appropriate patient information and education as well as patient motivation are necessary. Indeed, the patient needs to adhere and take an active part in order for this approach to be successful. Age does not seem to be a limiting factor to FT participation.[8]

Discharge from hospital and the patients return home require anticipated planning. To guarantee the success of a FT approach, hospital discharge criteria must be established and met as well as a homecare plan must be put into place. Commonly accepted discharge criteria are:

- Lack of organ dysfunction
- Afebrile condition
- Simple effective analgesia
- Normal feeding
- Independent mobility
- Patient consent

The patients social network must be evaluated and support by a health aide or a visiting nurse can be introduced if necessary. Medical follow-up must also be organized beforehand.

What are the expected benefits of "Fast track" surgery?

FT surgery facilitates the aftermath of surgery and presents an overall benefit for patients, caregivers and the health care system as demonstrated in colorectal surgery.

Overall benefits, out of which we can note:

- Earlier rehabilitation
- Reduced hospitalization length
- Decreased hospital and public health costs
- Patient satisfaction
- Reduced postoperative complications (infections, pulmonary pathologies, ileus, ...)

A preoccupation could be an increase in readmission rate but this hypothesis is invalidated by various studies.[9-11]

What are the current use and benefits of 'Fast track' in gynaecological surgery?

A recent review of the literature shows that the use of FT setting is only marginal in gynaecological surgery with some 30 publications identified to date in the 'Medline' and 'Ovid' databases as well as the 'Cochrane' library, most of which concern anaesthetic care. Indeed, no study has actually compared FT with conventional setting in gynaecological surgery and a fortiori no controlled randomized trial is found to bring a level of evidence sufficient to its wider implementation. The use of FT programs in gynaecological surgery however appears to be effective in reducing length of hospitalization in abdominal and vaginal hysterectomies as well as in vaginal surgery for prolapse.[12-14] A small-size descriptive study was carried out by Möller and Co and published in 1998.[12] Thirty-two patients allocated either to abdominal hysterectomy (n = 16) or laparoscopically assisted vaginal hysterectomy (n = 16) benefited from FT setting. The results showed shorter hospitalization for laparoscopically assisted vaginal hysterectomy of 1 day and 2 days for abdominal hysterectomy. These results are encouraging in comparison to the length of hospitalization in classical setting which are usually doubled. Another small-size descriptive study including 41 patients carried out by Ottensen and Co[13] and published in 2002 showed postoperative hospitalization of 24 hours after vaginal surgery for utero-vaginal prolapse in a fast track setting with no readmission occurred.

A synthesis of the results published in different studies regarding hospitalization length in FT setting shows a benefit in abdominal hysterectomy by laparotomy (Figure 2). No data was found for hysterectomy by laparoscopic approach.

Figure 2

Hospitalization length in conventional and "Fast track" setting (in days)		
	Conventional setting	**"*Fast track* " setting**
Abdominal hysterectomy	3.8[15] - 5.1[16]	1.9[17]- 2.6[18]
Laparoscopic hysterectomy	1.8[18] - 3.9[16]	Not available

In gynaecologic oncology surgery, a FT setting seems to be beneficial in patients operated for ovarian malignancy.[19-21] However, a recent Cochrane review showed that there was no evidence from high quality studies to support or refute the use of perioperative enhanced recovery programmes for gynaecological cancer patients.[22]

The aspects of financial benefit for hospitals and public health have not been assessed. High quality studies evaluating patient satisfaction or benefits in terms of quality of life cannot be found.

Conducting a randomized clinical trial in gynaecological surgery comparing FT and conventional setting in laparoscopic hysterectomy for benign indication, laparoscopy currently being the privileged way of access, is necessary to evaluate FT setting efficiency. The results of such a study could have major impact in perioperative care whilst demonstrating financial benefit for public health and patient satisfaction without changing complication and readmission rates. This is even more relevant in Switzerland, a country with a health care system combining fee for service and universal health insurance coverage, and where national health costs accounted for 11.5% of GDP in 2012 and are estimated at 16.7% of GDP in 2030.[23]

Hypothesis and objectives:

- Hypothesis:

The concept of "Fast track" which has proven its effectiveness in colorectal surgery is applicable in gynaecological surgery.

Perioperative "Fast track" setting is more efficient than conventional setting in laparoscopic hysterectomy for benign indication.

- Objectives:

The main objective of this study is to evaluate effectiveness of the "Fast track" concept in laparoscopic hysterectomy for benign indication in comparison to conventional setting in terms of cost and patient satisfaction. Earlier rehabilitation, diminution in hospitalization length and stable postoperative morbidity (number of thromboembolic events, number of infections, readmission rate) will be verified.

Methods:

- Design:

Randomized control trial: the randomization in two groups will be performed by computer using block of different sizes (2 and 4) before patient inclusion. Sealed, opaque and numbered envelopes will be prepared and patients will be included consecutively.

- Population:

All patients in our gynaecology department, in whom an indication of total or subtotal laparoscopic hysterectomy for benign indication with or without adnexectomy has been established (including robot-assisted interventions), will be proposed this study.

Exclusion criteria:

Patients needing an additional surgical procedure such as a prolapse surgery or urinary incontinence surgery as well as malignant pathologies will not be included in the study due to prolonged operative time which could compromise early home return. Non-French speaking patients will also be excluded from the study due to the necessity of their collaboration in filling a logbook drawn up in French on a daily basis during their hospitalization.

- Recruitment:

During pre-hospitalisation visit where surgical indications are established, eligible patients will meet a research nurse who will explain the study giving patients oral and written information. If the patient agrees to participate in the study, she will be included randomly in one of the two groups after having signed a consent form. She will immediately be informed of her allocation to the "Fast track" or the control group in order to best prepare her personal perioperative planning.

To increase the number of patients recruited, patients that meet the criteria of the study but who were not informed during the pre-hospitalisation visit will be contacted by a research nurse after the weekly colloquium of surgical indications, colloquium where all surgical indications of the department of gynaecology of the HUG are confirmed.

- Intervention:

Two types of perioperative settings will be compared:

○ Group 1: "Fast track" protocol

○ Group 2: conventional setting

1) "FAST TRACK" protocol

Preoperative evaluation and information:

○ Patient information of the study during the pre-hospitalisation visit and patient consent to participate in the study prior to hospitalization.

○ Patient general health state optimization proposal prior to hospitalization:

- Smoking cessation, if necessary (specialized consultation)
- Weight loss, if necessary (nutrition consultation)
- Patient autonomy and social environment evaluation (home care proposal if necessary)

Preoperative strategy:

- Hospitalization on surgery day
- No prolonged fasting (solids stopped 6 hours before surgery and liquids encouraged up to two hours before surgery)

Perioperative strategy:

- Anti-infectious prophylaxis: Cefazolin 2g IV
- Pain control based on limited systemic opioid therapy use
- Anti-nausea prophylaxis: 4g Dexamethasone preoperative + 4mg Ondansetron postoperative
- Fluid balance
- Anaesthesia via IV propofol / remifentanyl
- Bladder catheter removal postoperative

Postoperative strategy:

- Pain control using balanced analgesia
- Gum chewing
- Antithrombotic prophylaxis by low-molecular-weight heparin (40mg/60mg, depending on patient weight, 6 hours post-op during entire hospital stay)
- Early oral refeeding (as of 4 h postoperative)
- Rapid mobilization (as of 4 h postoperative)
- Venflon removal 6 hours post-op
- Standard criteria for hospital discharge the day after surgery, checked by a physician:
  - Lack of organ dysfunction (evaluated by physical examination)
  - Afebrile condition
  - Simple effective analgesia
  - Normal feeding
  - Independent mobility
  - Patient consent
- Planned outpatient follow-up: stitches/ skin staples removal on day 7, postoperative check-up on day 30
- Home care if needed

The protocol will have to be well-known by surgeons, anaesthetists and the nursing team.

2) «Conventional setting» protocol

Pre-hospital assessment

○ Surgical indication determination and surgical procedure explanation

Preoperative strategy:

○ Hospitalization on surgery day

○ Fasting as of midnight prior to the day of surgery

Perioperative strategy:

Treatments according to the surgeons and the anaesthesiologists practice:

○ Anti-infectious prophylaxis: Cefazolin 2g IV

○ Balanced anaesthesia via halogens gases

Postoperative strategy:

○ Mobilization depending on patient's general condition, on the evening of the surgery, at minimum 6 hours post operation

○ Antithrombotic prophylaxis by low-molecular-weight heparin (40mg/60mg, depending on patient weight, 6 hours post-op during entire hospital stay)

○ Same day refeeding, depending on the patient's general condition and according to her desire, proposed on the evening of the surgery at minimum 6 hours post operation

○ Bladder catheter and Venflon removal on day 1

○ Standard criteria for hospital discharge the day after surgery, checked by a physician:

- Lack of organ dysfunction (evaluated by physical examination)
- Afebrile condition
- Simple effective analgesia
- Normal feeding
- Independent mobility
- Patient consent

○ Planned outpatient follow-up: stitches/ skin staples removal on day 7, postoperative check-up on day 30

○ Home care if needed

- Issues:
  - Main:
    - Total costs: hospitalization costs and costs during the first month after surgery (ambulatory, home care and family/friends loss of earnings) (1)
  - Secondary:
    - Patient satisfaction (2)
    - Earlier rehabilitation (3) : pain comparison via pain scale (0-10) and resumption of normal bowel function via day of first stools and gas post-op
    - Morbidity during the first post-operation month (4):
      -readmission rate
      -number of infections
      -number of thromboembolic events

In order to measure the impact of the intervention on our practice, the length of hospitalization "Fast track" and conventional setting will be compared.

- Instruments:

1) Costs of the two types of setting ("Fast track" and classic) will be compared taking into account hospitalization and ambulatory costs which will be obtained via the patient EDS number as discussed with the medico-information department (Mrs. Claudine Bréant). In addition, home care will be accounted for via invoices and family/friends loss of earnings will be calculated based on the number of absent working days. With Switzerland's median wage of CHF 6118 per month in 2012 and approximately 21 working days per month, we can estimate a median wage of CHF 291 per working day.[24]
2) Patients satisfaction in both groups will be evaluated via a satisfaction questionnaire on their day of return home and at their follow-up visit one month after surgery.
3) Patients will be given a logbook questioning them on their pain awareness, their digestion and their mobilisation during their hospital stay.
4) Morbidity during the first month post-operation (i.e. readmission rate, number of infections and number of thromboembolic events) will be evaluated via the medical staff case report form.

A medical staff case report form containing their detailed clinical pathway will be used to verify patient's adhesion rate at each stage of the protocol.

A care map for each group will be used by the medical staff as a synopsis of the clinical pathway and will have to be signed by each medical intervener (nurse, gynaecologist and anaesthetist).

- Sample size

Sample size is calculated based on the difference of means for total costs in between the two groups including hospitalization costs and costs during the first month after surgery (ambulatory, home care and social environments loss of earnings). The null hypothesis tested will be that costs are identical in the two groups.

In order to obtain a power of 90% for type I error with a significance threshold at 0.05 in a two-tailed distribution and in order to highlight a difference equal to 0.5 standard deviations which is clinically relevant, the study will need to include 170 patients (n1 = 85; n2 = 85). Assuming an average cost of CHF 10'000 per hysterectomy for benign indication (CHF 12'809 in 2013, information given by Dr Peter Rohner, financial medical controller), it will be possible to highlight a statistically significant difference of CHF 1400 per surgery corresponding to 10% of the total amount which would be considered as clinically relevant.

- Type of analysis

The two groups will be compared in terms of their background characteristics which could influence study outcome. Factors such as age, BMI, hypertension, diabetes, and smoking will be taken into consideration. Patients adhesion rate at each stage of the protocol in the 'Fast track' group will also be evaluated. Special attention will be given to hospitalization length in the two groups.

Data will be analysed by the intention-to-treat approach. Patients will remain in the group to which they were initially allocated to at the beginning of the study.

Total average costs between the two groups will be compared using a T-Test with a 95% confidence interval. In the same way, global and per intervention patient satisfaction will be analysed with a T-Test even though they do not follow a normal distribution (right-tailed distribution). A second total average cost analysis will also be performed excluding patients who presented major perioperative complications requiring for instance intensive care unit which may influence study outcome with no direct relation to "Fast track" protocol.

Readmission rate, number of infections and number of thromboembolic events will also be compared between the two groups in terms of risk differences with a confidence interval of 95%. If these complications are sufficiently numerous, a Fisher's test will be used for comparison.

Ethics:

The study protocol will be submitted to the ethics committee of the Geneva University hospital (HUG). If approval is given by the ethics committee, all patients with a surgical indication of laparoscopic hysterectomy for benign indication in the gynaecology department of the HUG will be proposed to participate in this study. Eligible patients will receive oral and written information by a research nurse. Study participation will be voluntary and participants will be free to withdraw from the study at any time. Written consent will be given before inclusion in the study.

To ensure patient confidentiality, once a patient accepts to participate in the study she will receive a study number on a first-come, first-served basis. For instance Mrs Dupont, 58th participant will be known under patient 58 irrelevant of whether she has been attributed to the protocol FT or conventional. This number will be written on the patient information and consent form, the medical staff case report, the care map and the patient's log-book. The document containing the name of the patient paired with her study number (la main courante) will be kept under lock at the clinical research unit of the gynaecology department. Only the investigators and the research nurses will have access to this document.

The patient information and consent form, the medical staff case report, the care map and the patient's log-book will also be kept at the clinical research unit of the gynaecology department where only the investigators and the research nurses will have access.

Study participation presents no particular risk for patients since the "Fast track" concept has already demonstrated efficiency in colorectal surgery with no morbidity increase. Moreover, the various stages of the "Fast track" protocol are already commonly applied on a case-by-case basis in our current conventional setting. The choice to exclude from the study patients needing an additional surgical procedure such as a prolapse surgery or urinary incontinence surgery as well as malignant pathologies is justified by the fact that operating time is prolonged which could compromise homogeneity of the sample. Non-French speaking patients will also be excluded from the study due to the necessity of their collaboration in filling a logbook drawn up in French on a daily basis during their hospitalization.

A liability insurance policy will be issued in the name of the HUG by Me Marescotti (legal advisor) as soon as approval has been given by the ethics committee of the Geneva University hospital (HUG).

Logistics:

- Calendar

With an estimated patient eligibility of 140 laparoscopic hysterectomies for benign indication per year in the department of genecology of the HUG and a recruitment rate of one patient on two.

	1st year 2014				2nd year 2015				3rd year 2016				4th year 2017				5th year 2018			
Trimesters	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
General organization																				
Document preparation (logbooks and patient satisfaction questionnaire, ethics committee submission & agreement and fund raising)																				
Database preparation																				
Patient recruitment and data collection																				
Additional data entry																				
Analysis																				
Results and manuscript drafting																				
Publication																				

- Collaboration between surgeons, anaesthetists and caregivers

All interveners of the gynaecology department will be informed orally by the main investigator during an information session and by written. A copy of the study protocol will be sent by e-mail.

Anaesthetists will also be informed orally by the main investigator and a representative who already has experience in the “Fast track” concept will be officially appointed. A copy of the study protocol will be sent by e-mail.

Finally, the nursing team will also be informed in the same way and a representative will also be appointed.

- Funding:

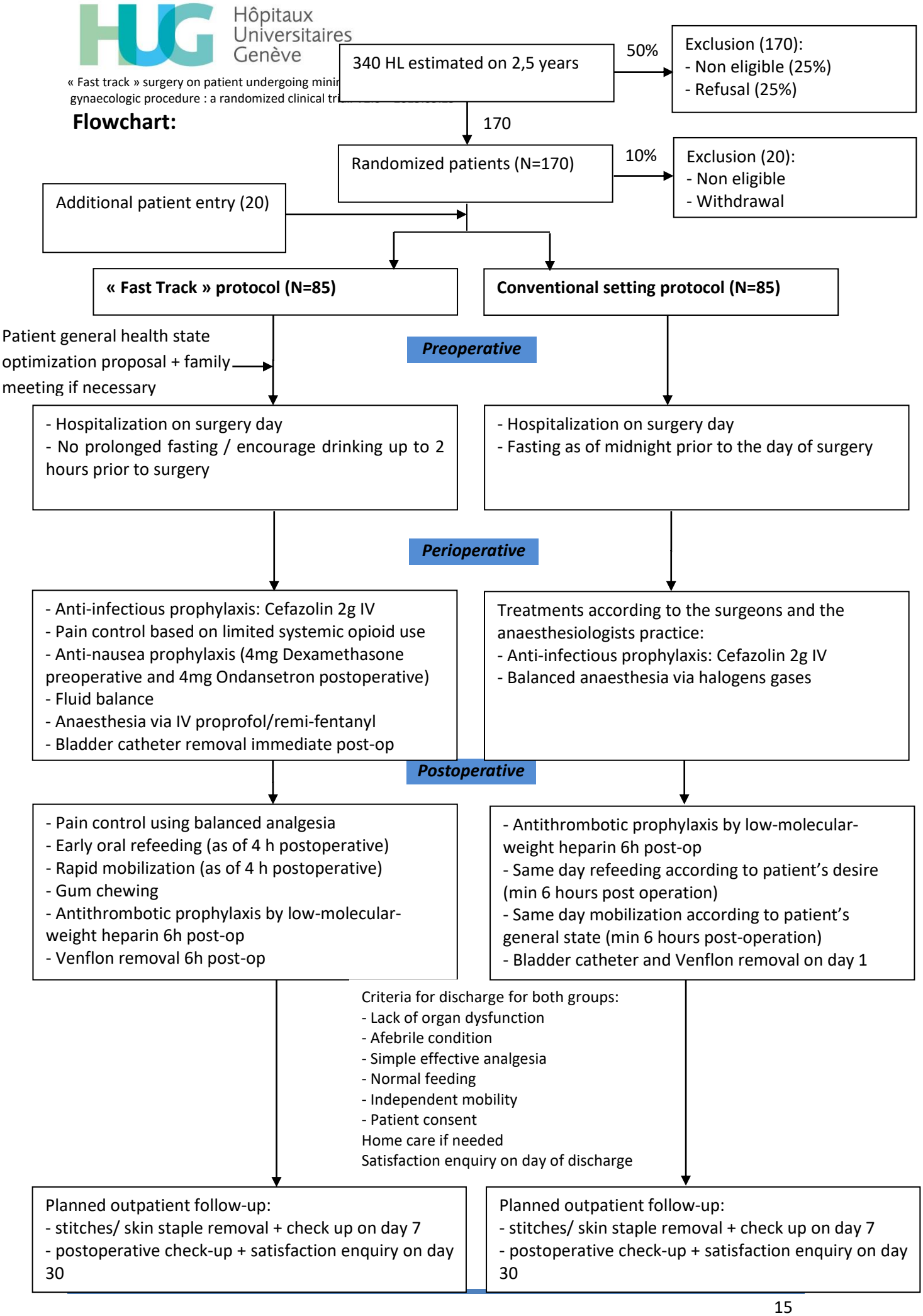
A funding application will be made to the medical direction of the HUG as part of a Research and development project with the purpose to gather the necessary budget:

- Two research nurses at 50% for two years and at 40% for the last 6 months (total of 200'000 CHF)

  Project to be submitted to Fondation privée des HUG

- Computing resources, office equipment and premises will be made available by the HUG.

Flowchart:


340 HL estimated on 2,5 years
50%
Exclusion (170):
- Non eligible (25%)
- Refusal (25%)
170
Randomized patients (N=170)
10%
Exclusion (20):
- Non eligible
- Withdrawal
Additional patient entry (20)
« Fast Track » protocol (N=85)
Conventional setting protocol (N=85)
Patient general health state optimization proposal + family meeting if necessary
Preoperative
- Hospitalization on surgery day
- No prolonged fasting / encourage drinking up to 2 hours prior to surgery
- Hospitalization on surgery day
- Fasting as of midnight prior to the day of surgery
Perioperative
- Anti-infectious prophylaxis: Cefazolin 2g IV
- Pain control based on limited systemic opioid use
- Anti-nausea prophylaxis (4mg Dexamethasone preoperative and 4mg Ondansetron postoperative)
- Fluid balance
- Anaesthesia via IV proprofol/remi-fentanyl
- Bladder catheter removal immediate post-op
Treatments according to the surgeons and the anaesthesiologists practice:
- Anti-infectious prophylaxis: Cefazolin 2g IV
- Balanced anaesthesia via halogens gases
Postoperative
- Pain control using balanced analgesia
- Early oral refeeding (as of 4 h postoperative)
- Rapid mobilization (as of 4 h postoperative)
- Gum chewing
- Antithrombotic prophylaxis by low-molecular-weight heparin 6h post-op
- Venflon removal 6h post-op
- Antithrombotic prophylaxis by low-molecular-weight heparin 6h post-op
- Same day refeeding according to patient's desire (min 6 hours post operation)
- Same day mobilization according to patient's general state (min 6 hours post-operation)
- Bladder catheter and Venflon removal on day 1
Criteria for discharge for both groups:
- Lack of organ dysfunction
- Afebrile condition
- Simple effective analgesia
- Normal feeding
- Independent mobility
- Patient consent
Home care if needed
Satisfaction enquiry on day of discharge
Planned outpatient follow-up:
- stitches/ skin staple removal + check up on day 7
- postoperative check-up + satisfaction enquiry on day 30
Planned outpatient follow-up:
- stitches/ skin staple removal + check up on day 7
- postoperative check-up + satisfaction enquiry on day 30

References

1. Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H. Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet. 1995 Mar 25; 345(8952): 763-4.
2. Basse L, Hjort Jakobsen D, Billesbolle P,Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. Ann Surg 2000;232:51-7.
3. Kehlet H,Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg 2002;183:630-41.
4. Kehlet H, Buchler MW, Beart RW, Billingham RP, Williamson R. Care after colonic operation – is it evidence-based ? Results from a multinational survey in Europe and the United States. J Am Coll Surg 2006; 202:45-54.
5. Fearon KC, Ljungqvist O,Von Meyenfeldt M, et al. Enhanced recovery after surgery : A consensus review of clinical care for patients undergoing colonic
6. Wind J, Polle SW, Fung Kon Jin PH, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg 2006;93:800-9.
7. Weimann A, Braga M, Harsanyi L, et al. ESPEN. Guidelines on enteral nutrition : Surgery including organ transplantation. Clin Nutr 2006;25:224-44.
8. Rumstadt B, Guenther N, Wendling P, et al. Multimodal perioperative rehabilitation for colonic surgery in the elderly. World J Surg. 2009 Aug;33(8):1757-63.
9. Eskicioglu C, Forbes SS, Aarts MA, Okrainec A, McLeod RS. Enhanced recovery after surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. J Gastrointest Surg. 2009 Dec;13(12):2321-9.
10. Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer.Ann Surg. 2007 Jun;245(6):867-72.
11. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg. 2008 Aug; 248(2): 189-98.
12. Moller C, Kehlet H, Friland SG, et al. Fast track hysterectomy. Eur J Obstet GynecolReprodBiol. 2001 Sep; 98(1): 18-22.
13. Ottesen M, Sorensen M, Kehlet H, Ottesen B. Short convalescence after vaginal prolapse surgery. Acta ObstetGynecol Scand. 2003 Apr; 82(4): 359-66.
14. Ottesen M, Sorensen M, Rasmussen Y, et al. Fast track vaginal surgery. ActaObstetGynecol Scand. 2002 Feb; 81(2): 138-46.
15. Van Bree S, Vlug M, Bemelman W, Hollmann M, Ubbink D, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. Gastroenterology. 2011 Sep;141(3):872-880.
16. Feroci F, Kröning KC, Lenzi E, et al. Laparoscopy within a fast-track program enhances the short-term results after elective surgery for resectable colorectal cancer. SurgEndosc. 2011 Sep;25(9):2919-25.
17. Borendal Wodlin N, Nilsson L, Kjøhede P; GASPI Study Group. The impact of mode of anesthesia on postoperative recovery from fast-track abdominal hysterectomy: a randomised clinical trial. BJOG. 2011 Feb; 118(3): 299-308.
18. Pather S, Loadsman JA, Mansfield C, Rao A, Arora V, et al. Perioperative outcomes after total laparoscopic Hysterectomy compared with fast-track open hysterectomy- a retrospective case-control study. Aust N Z J ObstetGynaecol. 2011 Oct; 51(5): 393-6.
19. Cascales Campos PA, Gil Martinez J, Galindo Fernandez PJ, Gil Gomez E, Martinez Frutos IM, et al. Perioperative fast track program in intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery in advanced ovarian cancer. Eur J SurgOncol. 2011 Jun; 37(6): 543-8.
20. Marx C, Rasmussen T, Jakobsen DH, Ottosen C, Lundvall L, et al. The effect of accelerated rehabilitation on recovery after surgery for ovarian malignancy. ActaObstetGynecol Scand. 2006; 85(4): 488-92.
21. Chase DM, Lopez S, Nguyen C, Pugmire GA, Monk BJ. A clinical pathway for postoperative management and early patient discharge: does it work in gynecologic oncology? Am J Obstet Gynecol. 2008 Nov;199(5):541.
22. Lv D, Wang X, Shi G. Perioperative enhanced recovery programmes for gynaecological cancer patients. Cochrane Database Syst Rev. 2010 Jun 16; (6): CD008239.
23. Office fédérale de la statistique : Déterminants et évolution des coûts du système de santé en Suisse. Revue de la littérature et projections à l'horizon 2030. Last accessed 17.06.2014. http://www.bfs.admin.ch/bfs/portal/fr/index/news/publikationen.html?publicationID=2930
24. Office fédérale de la statistique : Enquête suisse sur le niveau et la structure des salaires 2012: premiers résultats. Last accessed 17.06.2014. http://www.bfs.admin.ch/bfs/portal/fr/index/news/medienmitteilungen.html?pressID=9416.