Case study
GynOcclude, a minimal-invasive medical device to treat uterine fibroids

Clinical Development On-campus
**Background**

Identifying those novel interventions in an R&D project that are unlikely to reach the patient and stopping their development as soon as possible, brings big rewards. For this reason, more and more effort is being put into the early selection of promising new interventions, for example, by including informative biomarkers in the initial stages and introducing early proof of principle studies.

Another way is to value each R&D project in a company’s pipeline in advance, usually by calculating their respective net present values (NPV), as we have seen in the online course. The highest NPV is achieved by projects with the highest estimated market value combined with the lowest development costs and shortest time to registration. NPV analysis or risk-adjusted NPVs are also frequently used by large companies when acquiring novel technology from smaller companies.

The problem with the NPV approach is that while it can optimize the many procedural aspects of development, including time and costs, it lacks a clear way to valuate critical knowledge. Introduction of additional (clinical) studies merely reduces the NPV value of a development project. Obviously including extra tests in the project will increase the development costs, but it can also lower the risk for an expensive failure later in the development process. For some reason, managers can communicate numerically about procedural aspects but when it comes to the content of their project, any discussion about the probabilities of certain events occurring is done intuitively and not incorporated in value estimations. One matter that has not been dealt with adequately is the integration of both the procedural and the knowledge aspects of the development of a novel medical intervention. As we have seen in the online course, a question-based approach to clinical development will integrate the two into a comprehensive concept.

Similar to other efforts, NPV analysis is an attempt to deal with the uncertainties and risks of clinical development in a procedural approach. A question-based approach to clinical development seems more rational and better incorporates the alteration of success probabilities. Furthermore, the question-based approach has implications for the design and execution of the clinical development project and the selection and acquisition of novel medical interventions.
The examples presented in the online course illustrated that the combination of success probabilities and accompanying costs to answer the questions are a unique data set that can vary with different intervention types. Even if the overall probability of success and the overall costs are the same, these unique sets dictate an optimal development strategy. The sequence of relevant questions should serve as a priority list in the development of new medical interventions throughout the development program. Regular updates of all probabilities and costs will optimally direct the development process. Another advantage of the question-based approach is that experts of different company departments involved in the development of novel medical interventions discuss and agree on the chances and threats in the development of the intervention. In more advanced calculations, the question based approach calculations can be performed using NPV estimations, thus also correcting for time effect on capital expenditures and earnings.

In the online course we have introduced this QBCD method and the QOC as a simple tool to prioritize up to 6 user defined questions. The algorithm used in the QOC translates the Real Options Theory into a versatile tool which can optimally order up to six R&D questions. It can therefore be considered to be Futurelab’s critical path finder.

As we have seen in the online course each of these questions has a probability to be successfully answered but answering these questions will introduce development costs. The set of probabilities and costs varies for each medical intervention and is therefore unique. For one intervention it can be very difficult to successfully answer the ‘site’ question, whereas it can be relatively easy for another intervention, such as in this case.

The Real Option Theory approach takes into consideration the fact that projects can also be discontinued at various stages of the development program. The early discontinuation of a novel intervention that will be unsuccessful is desirable and the value of early evaluation studies on relevant questions can be incorporated in the analysis.

The QOC introduces a question-based approach to clinical development which uses decision knots that are relevant for the development of new interventions: generic questions that are really answered throughout the development program. The resulting question-based decision tree reflects the true risks and uncertainties that are faced in the development of an individual intervention. With five key questions the QOC analyses the 120 different question sequences \((5! = 120)\) and returns the sequence with the highest project value as the optimal route.

Furthermore, the question-based approach shows how the project value can increase by performing an additional early stage study that helps to adequately answer a
question later on. These studies can help in preventing unsuccessful compounds to enter late stages of development after substantial costs have been incurred. This approach can be used for the development of intervention types such as pharmaceuticals, medical devices or medical nutrition.

The early discontinuation can substantially reduce the costs of the development of novel interventions. By defining the costs and probabilities of success and constructing the decision tree for a new product, the bottleneck in the development of each individual product will be identified.

Before class, please read the following documents:

1. Attachment 1. Developing GynOcclude to treat uterine fibroids

Additional information (Optional)

4. If you want to refresh your memory on Question Based Clinical Development, you may want to have a look back at the online course Clinical Development https://www.pauljanssenfuturelab.eu/courses/clinical-development-online/.
5. Fibroids, Menstruation, Childbirth, and Evolution; The Fascinating Story of Uterine Blood Vessels by Fred Burbank, MD, FSIR
Assignment

In this simulation you and your team will act as the global development team of the medical device company Ethicon, Inc. part of Johnson & Johnson. The company has recently acquired GynOcclude, a promising medical device to treat uterine fibroids in a less invasive way.

You are provided with a basic outline of what is known about the intervention so far. You and your team will use the QBCD approach to discuss and outline a development plan for this device and advice the board of directors of Ethicon how to invest in it. As you now know the optimal order of addressing research questions in the development program is dependent on the estimated success chance and efforts (i.e., costs) needed to answer the question. The first task for your team is therefore to discuss which key questions you think are most relevant here (you may or may not use the generic set of 5 default QOC questions) and discuss how the overall development risks and efforts in your opinion are divided over the questions for this device.

The rules are that you are not allowed to alter the overall success chance (the board and the financial department of your company used a 40% overall success chance to launch this device, which is what we will use). What matters most is how you think the risks of answering the questions accumulate to this success chance i.e., the breakdown over the individual questions. You may come up with other questions than the generic five main questions. You are allowed to spend an additional 40 M$ on answering these questions successfully. The estimated revenues are set at 1000 M$. Again, what matters most is how you (roughly) estimate these Dollars should be allocated to the questions. Use the Questions Optimizing Calculator for this assignment. You will present your priority list and, more importantly, share your thoughts on where the development risks lay for this device in your opinion.
Second part of the assignment will be to back translate an optimized order of questions to a (clinical) development program. Your task as a development team is to present an outline of (clinical) studies that you want to perform to answer the critical questions you identified in the first assignment. Remember, one question can be concealed in several studies or one study can address multiple questions. The faculty staff will represent the board of directors of the company that develops the device so be convincing!
Attachment 1

Developing GynOcclude to treat uterine fibroids
Medical device information

From creating the first sutures, to revolutionizing surgery with minimally invasive procedures, Ethicon, Inc., part of the Johnson & Johnson Family of Companies you work for, has made significant contributions to surgery for more than 60 years. Ethicon’s continuing dedication to shape the future of Surgery is built on its commitment to help address the world’s most pressing healthcare issues, and improve and save more lives. Through Ethicon’s surgical technologies and solutions including sutures, staplers, energy devices, trocars and hemostats and its commitment to treat serious medical conditions like obesity and cancer worldwide, it delivers innovation to make a life-changing impact.

In 2006, while you just started working for Ethicon, Inc., you read the following press release:

The leading technology referred to here is GynOclude, a Doppler-Guided Uterine Artery Occlusion (D-UAO) Device to treat uterine fibroids. You and your team at Ethicon, Inc. are to develop this device through clinical development to a successful launch of the product worldwide.
Unterine fibroids

Symptomatic uterine fibroids are a relatively common gynecologic condition. Due to the high unmet need for symptomatic fibroid patients, the burden on Quality of Life (QOL) and the need to treat these patients, the board decided there is an excellent business case to acquire this technology. It is estimated that worldwide ~3.9 million women are diagnosed with this condition. In the past, fibroids were exclusively treated by invasive myomectomy and/or hysterectomy. With the advent of uterine artery embolization or uterine artery occlusion, minimally invasive approaches are being developed to fibroid therapy especially for women in whom surgery is contraindicated or for those who wish to retain their uterus and possibly fertility. Extensive background information is optionally available in the online course material; *Fibroids, Menstruation, Childbirth, and Evolution*: The Fascinating Story of *Uterine Blood Vessels* by Fred Burbank, MD, FSIR [5] who is the main inventor of GynOcclude and owner of Vascular Control Systems Inc., the company that was acquired by Ethicon, Inc.
Gynocclude

The proposed mechanism of action of GynOcclude is - in short - based on transient uterine ischemia. Uterine arteries contribute to most of the uterine blood supply. The blood flow to the uterus can be blocked (occlusion) by GynOcclude. During occlusion vessels within the myometrium clot turn hypoxic and collateral arteries begin to reperfuse uterus. Within hours to days clots are lysed. While the uterus can lyse clots and reperfuse, myomas cannot lyse clotted blood and subsequently fail to reperfuse. This causes selective infarction and myoma death. In the course materials you will find a review article about this principle; Uterine artery occlusion: what is the evidence? Vilos GA1, Hollett-Caines J, Burbank F. Clin Obstet Gynecol. 2006 Dec;49(4):798-810 [2].

A short movie clip describing how the principles of occlusion works in treating uterine fibroids is available in the online course materials [3]. Ethicon, Inc. acquired this technology in 2006 for 105 M$ and the business case was presented to the board with several slides including the following, highlighting the target product profile, the acquisition model, market model and a decision tree.

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**Slide 2.** Comparison of the Doppler-guided uterine artery occlusion intervention with the standard hysterectomy for the treatment of fibroids. Class IIB and class III represent the device classes in the European Union and the USA respectively. AE = Adverse Event; ASP = Average Selling Price; D-UAO = Doppler-guided Uterine Artery Occlusion; EMEA = Europe, Middle East and Africa; FAS = Fibroid-Associated Symptoms; IP = Intellectual Property;

Slide 4. World wide market model for GynOcclude with an estimation of the number of patients that are eligible for a treatment with GynOcclude.
Slide 5. Target indication and potential follow-on indications of Doppler-guided Uterine Artery Occlusion

Obviously, this decision tree is only the start of subsequent discussions in your group. Refinement of this tree is asked for by senior management and you will have work towards defining the critical questions and how to address them for future development. Thankfully, you have access to the QOC tool allowing you to transparently discuss what you think the main critical questions are for this particular intervention.

To facilitate the discussion and efficient group work in the on-campus course each participant will individually prepare an analysis using the Questions Optimizing Calculator (QOC) for this case study as a preparatory assignment and upload the result before Thursday May 31, 12:00 CET.

In the on-campus working group sessions each group will decide on a definite analysis. Next, this group-QOC will be the basis for an outline clinical development plan which you will present to the Board of Ethicon, Inc.