A) Cover Page

1) Title: Improvement of diagnosis and treatment of adulthood post radiation GH deficiency in survivors of childhood cancer

Grant ID number: 34584213

Main collaborators:
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Department of Pediatric Endocrinology, Hôpital Bicêtre, Le Kremlin Bicêtre, France: Dr Cécile Thomas-Teinturier
Inserm, Centre for research in Epidemiology and Population Health, UMR1018, Cancer and radiation Team, Institut Gustave Roussy, Villejuif, France: Florent de Vathaire, Agnès Dumas
Club Français de l’Hypophyse
Société française d’endocrinologie
Société française d’endocrinologie et diabétologie de l’enfant
Société française de cancérologie de l’enfant
Patients’associations: “Les aguerris”, “Grandir” and “Craniopharyngiomes Solidarité”

2) Abstract:

The goal of this project is to improve the quality of medical management of adult survivors of childhood cancer, in terms of assessment and treatment of pituitary and GHD deficiency.

Methods: To create a website providing information on childhood cancer’s late endocrine sequelae and a free MOOC dealing with post-radiation pituitary deficiency and its treatment over life and to offer on-line support and guidance to patients, relatives and medical practitioners in order to assess its efficiency in terms of percentage of patients that would be referred in Endocrinology departments and decrease in patient follow-up lost rate during transition and improve quality of information and level of health education in survivors and GPs about the long term consequences of their deficiencies.

Assessment: The satisfaction with the content, usability and design of the MOOC will be studied by a specific questionnaire completed at the end of the training. The number of website visits will be counted as well as the number of registrations to the MOOC.
To evaluate the improvement in the rate of survivors who restart endocrine follow-up, or who remain on GH therapy after adolescence, a specific questionnaire will be sent to every participant in the MOOC, 6 and 12 months after their participation.
The perceived improvement in knowledge about childhood cancer late endocrine effects in survivors and medical practitioners will be addressed by the analysis of the difference in the quiz answers before and after the specific training with the MOOC.
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C) Reviewer Comment

Comment 1: « The panel members did suggest that plans for long-term maintenance and update of the database be included in the full proposal »:
We explain on page 8 that the MOOC and webpage will be available for free with no time limit. This project is not intended to create a database.

Comment 2: « as well as a more detailed description of the MOOC and further information on how to evaluate the success of the MOOC ». See page 8-10

Comment 3: « The QoL tool used to show impact on patient and measured physician practice change should be identified, and the organisation’s experience of using the tool described. »
This project is not intended to show impact on QoL of cancer survivors but on their knowledge on pituitary deficiency and growth hormone therapy. The questionnaire that will be used to measure physician practice change is not yet available but the first basis is detailed on page 10 . A secondary analysis of the impact of these patients’ medical care change on their QoL will be considered at longer term. It is not planned in this funding request because it would require a longer follow-up. We rely on the epidemiology team (Agnès Dumas and Florent de Vathaire) expertise of using these tools in social research. See their biographical sketches in appendix.
D) Main Section of the proposal

1) Overall Goal & Objectives:
The goal of this project is to improve the quality of medical management of childhood cancer survivors when they reach adulthood, in terms of assessment and treatment of pituitary deficiency, particularly growth hormone deficiency (GHD).

a) Hypothesis:
Most of Growth Hormone (GH) deficient adult patients due to childhood cancer treatment are lost to endocrinological follow-up after pediatric care because of a lack of information on the benefits and absence of risks of GH therapy in this population of survivors. Individuals who are better informed are more likely to adopt health-protective behaviors (such as undergoing regular medical checkups or compliance to their treatments). Informing General Practitioners (GP’s) should favor the referring of these patients to endocrinology services.

b) Main objective:
To create a website providing information on childhood cancer’s late endocrine sequelae and a free MOOC (Massive Open One-line Course) dealing with post-radiation pituitary deficiency and its treatment over life and to offer on-line support and guidance to patients, their relatives and medical practitioners.

c) Secondary objectives:
To assess the usability of this website and MOOC and its efficiency in terms of percentage of patients that would be referred in Endocrinology services as well as satisfaction of users.
To improve the quality of care during transition period in order to limit as much as possible loss of follow-up.
To improve quality of information and level of health education in survivors and GPs about the long term consequences of their deficiencies.

d) Adequacy with the focus of this RFP and our departments

Our goal fits perfectly with the focus of this RFP, by trying to improve patients’ and GPs’ awareness and knowledge about post-radiation GHD in survivors of childhood cancer. A better knowledge of risk factors associated with the development of GHD, of which patients may be concerned by this particular condition and of the long term consequences of not being treated should favor a new patient care in endocrinology for those patients who have been lost to follow-up for many years. Our departments of adult and pediatric endocrinology are located in the same hospital and we are used to work together, particularly during the transition period where adolescents stop their treatment with GH for reassessing GH secretion and associated pituitary deficiencies. Our two departments have developed a high level of expertise in pituitary diseases and have been recognized in 2017 as a national reference center for rare pituitary disease. Moreover, also in 2017, our Center has been approved at the European level as an expert Center of the European Rare Endocrine Diseases Network (ENDO-ERN), after a call launched by the EU.

2) Current Assessment of need in target area
Progress in cancer treatment in childhood have led to major improvements in survival (1). Nowadays, more than 70% of children treated for cancer will survive. Annual incidence rate of cancer in childhood is 150 cases per million. It can be estimated that roughly 1 out of 750 young adults aged 20 to 30 is a childhood cancer survivor. Data from the US cohort have shown that among survivors, the cumulative incidence of a chronic health condition reached 73% 30 years after the cancer diagnosis, with a cumulative incidence of 42% for severe, disabling, or life-threatening conditions (2). Endocrine sequelae are among the most frequently reported complications in childhood cancer survivors, affecting 40 to 60% of these patients during adult life (2, 3, 4). According to Scandinavian registers, the cumulated risk of endocrine dysfunction might reach 43% at the age of 60 in survivors treated for cancer between the age of 5 and 9 years (5). Growth hormone deficiency (GHD) occurring after cranial irradiation involving the hypothalamo-pituitary region, is the first (and often the only) pituitary deficiency to develop during childhood (6). Endocrine pathologies notably contribute to morbidity in these patients (2). In adults, GHD is associated with altered quality of life, increased fracture risk and deleterious cardiovascular risk profile related to the increased fat mass, particularly visceral. GHD is also associated with decreased left ventricular mass. Many studies have evaluated metabolic benefit associated with GH treatment but few concerned childhood cancer survivors. One group has shown that 5-years GH therapy was associated with blood glucose decrease, improvement in lipid profile, reduction of prevalence of metabolic syndrome but no modification of left ventricular function and quality of life (7). Another study, but on a small sample of patients, showed a positive effect on bone mineral density after 2 years of treatment (8) and another demonstrated an improvement in quality of life (9).

To obtain figures about survival, compliance and treatment with GH in adulthood in France in patients treated for cancer during childhood, we analyzed a first sample of 150 patients of the cohort “EuroK” treated for cancer in childhood before 1986 in 3 sites: Institut Gustave Roussy in Villejuif, Institut Curie in Paris, and American memorial hospital in Reims. We also analyzed preliminary results of a survey performed in another sample of 263 patients treated before 2000 for their cancer in Institut Gustave Roussy and Institut Curie, during their childhood or adolescence. This allows to conclude that, in our cohort of cancer survivor patients evaluated at adulthood, around 30% of the patients have been lost to follow up, and only 5 to 13% are treated with GH on long term, because half of the patients in whom GH treatment was initiated have secondarily stopped it. The reasons of this low compliance are not well understood but certainly include defects in care organization and health professionals/patients education.

In this setting, it is interesting to note that in our survey, only 19 out of 263 patients who received GH during childhood answered “Yes” to the question “Do you have pituitary insufficiency?”…!

Studies on information needs of childhood cancer survivors have shown that, as a priority, childhood cancer survivors want information about late effects and how to deal with them (10-13). While the scientific knowledge on late effects of cancer treatments has expanded, availability of information for the lay public on late effects seems very limited in France, as compared to other countries. Only one leaflet, produced by the SFCE (The French society for childhood and adolescent cancer) clearly explains these risks and enumerates symptoms “that should alert” but nothing is written on post radiation pituitary deficiency. Other information resources are written in English and/or in a scientific language that is not readily
accessible. This contrasts with several other countries such as the US or the Netherlands, where books and websites entirely dedicated to childhood or adolescence cancer survivorship have been created. Because the information is structured into a network of links, websites offer a more interactive and personalized way to provide information than books or booklets. Many cancer survivors turn to the Internet to find information (14). In a US study of children and adolescent cancer survivors, 95% of participants (age: 18-40) had used or wanted to use Internet sites that offer appropriate support (15). There has been a lot of innovation tools developed in this area during the past years that can be used to ensure increased comfort and overall improvement of quality of life of patients. Faced with increasingly connected patients and people with illnesses, the medical industry is continuously developing new technologies for better care. Being the precursor to telemedicine, eHealth is now developing rapidly.

3) Target Audience:

This project is first intended for adult patient survivors of childhood cancer and their relatives and general practitioners.

a) Plan for recruitment

For recruitment of our target audience, we need to make communications on medias and be referenced in Google. We have planned to create a webpage on endocrine sequelae of childhood cancer treatment and the link for the MOOC will be inserted in that page. A website has already been created for an epidemiological study on long-term outcome in survivors of childhood cancer for the French Childhood Cancer Survivors Study (FCCSS) http://fccss.fr/. The scientific director of this cohort is Florent de Vathaire and the responsible for the website is Agnès Dumas, all of them are actively participating in our project. So our webpage will be referenced in their website by a link in order to redirect survivors who suffer from endocrine sequelae. Cecile Thomas-Teinturier who is the endocrine referent in the late effect committee of the French Society for Childhood and Adolescent Cancer (SFCE) will ask this society to do the same in their webpage on late effects of their website http://sfce.fr. This will also be proposed on the website of the French Endocrine Society www.sfendocrino.org/ (Philippe Chanson is member of the Executive Committee) and on that of French Pediatric Endocrinology and Diabetes Society www.sfedp.org/. Communications during special sessions of the French Endocrine Society (SFE) and French Society for Pediatric Endocrinology and Diabetology (SFEDP) will be made to inform endocrinologists about this project. Special mailing and flyers will be sent to GPs, particularly those who are involved in sheltered workshops and centers for the disabled.

Flyers would be available and posters would be displayed in consultations for childhood cancer survivors and meetings organized by childhood cancer survivors associations. Information will be provided on the website of the various patients associations who already enthusiastically agree with the project. We will send information letters with the flyers to all childhood cancer survivors who already agreed to participate to the long term follow-up cohort FCCSS and said to have received growth hormone therapy during childhood.
b) **Demonstrate the scope of your target audience has a potential to impact the goal established in this proposal.**

As explained above, the high number of children lost to endocrine follow-up when they reach adulthood justifies the use of every possible means for reaching our goal. We obviously have to track the patients (i.e. returning to the list of patients treated, finding if their address remains the same or by contacting their parents if they always live at the same address), finding their new address, sending them a letter which will propose a consultation if they want but overall proposing them to be informed by modern ways : network of links, websites, MOOC which offer a more interactive and personalized way of providing information than books or booklets. However, we know that a simple contact from the institution that managed their cancer during childhood for offering the program will not be sufficient in many cases (and even could be “repulsive” for some of them!). This is why our objective, in some cases, will only be to suggest them that information is available in case they are interested. We already know that many cancer survivors turn to the Internet to find information and we want them to find good information which, if they need, will lead them to come into contact with us for evaluation and treatment.

c) **Who will directly benefit from the project outcomes?**

This project is directly dedicated toward a subpopulation of pituitary deficient patients, those who experienced pituitary deficiency after radiation therapy for a childhood cancer and its goal is educational. But the specific module of the MOOC on GH therapy could be used also for every GH deficient patient, nurse or GP who are involved in GH therapy whatever the etiology. If this way of recruiting patients who are lost to follow-up is valuable, then our project could serve as a model for a strategy to be developed in other chronic diseases where patients are non compliant or lost to follow-up after adolescence.

**4) Project Design and Methods:**

a) **Description of the organization and the content of the webpages on Endocrine sequelae after treatment for childhood cancer**

These webpages will be included in the website of our organization (APHP Hôpitaux Paris-Sud) in link with the page dedicated to the Departments of Adult Endocrinology and Pediatric Endocrinology. These webpages will be first intended for patients and their relatives, but will also include specific resources for health care professionals such as general practitioners (GP’s).

It will include internal resources on the different endocrine sequelae that can be expected after treatment for childhood cancer listed by organ i.e. pituitary, thyroid, gonads or disease i.e. growth, puberty, diabetes, obesity and osteoporosis. The text information will be provided through a search engine structure on late effects, accessible to all web-users, providing access to textual and visual information. A brief report in a language understood by the great majority will be available, as well as links to external resources such as press releases related to scientific studies and researches that we, collaborators or others have already published, information about support groups and patients associations and links to websites dealing with other late effects in survivors of childhood cancer.
The website will ask for a HON Code certification. The HONcode is the oldest and the most used code for medical and health related information available on Internet (http://www.hon.ch/HONcode/Conduct.html). An e-mail address will also be offered to allow any physician (GP’s, specialist) or patient who does not have a referent in endocrine sequelae to ask a question or to find a referent. The management of the e-mail address will be handled by a project manager and the involved clinicians.

A link to subscribe to the MOOC free of charge will be provided in the main website. The site host will be our organization, in order to carry out maintenance and continuing updating. Keywords index will be defined to spotlight our webpage on Google search for the web-users. So this webpage will be permanent.

b) MOOC on post-radiation pituitary sequelae

The MOOC on post-radiation pituitary sequelae will combine videos and texts with voices on pituitary sequelae. It will be elaborated by endocrinologists and pediatric endocrinologists for medical content, supervised by academics teachers and regularly checked by patients. Their computerized design will be done by scholar engineers well trained in e-learning. It will be adapted to be viewed by every childhood cancer survivors, whatever the treatment or late effects he or she has had. For GPs who will participate to the MOOC, in order to increase its attractiveness, we will ask competent professionnal authority to recognise this resource for ongoing education in order to offer continuing education credits for the GPs that will complete the MOOC.

For this project, the MOOC will be first running for 6 months. But even after these 6 months, it will be available permanently on the hosting website, so every web-users can read it, but without moderator. Moreover, we could make it running for other periods of time if this tool is valuable and workable.

Registration modalities
The registration to the MOOC will be free of charge and only require a valid email address and the answer to one question “are you a patient, a relative or a GP?”. This email address will be kept in a database in order to identify the participant, his answers to quiz and later to send him (her) a questionnaire for analysis of this tool efficiency.

Content of the MOOC
This MOOC aims to help to acquire knowledge on pituitary deficiency after radiation therapy, exchange informations with medical experts in this field, listen to their recommendations on appropriate investigations and follow-up and learn about GH treatment modalities.

It will be built in 4 modules, each module is independent and will be preceded and followed by a quiz, in order to test the acquired knowledge and its impact on the desire of patients to be referred -or of GPs to refer their patients- to Endocrinologists. Quiz will include 5 to 10 true or false questions in each module.

Module 1: “What is pituitary deficiency after radiation therapy?”
Its objectives are to increase knowledge on pituitary deficiencies : who is at risk after radiation therapy (which doses, what kind of radiotherapy, how long after radiation therapy...), symptoms related to each deficiency, how to diagnose them...
Module 2: “All you want to know on GH therapy”
This will be a typical training on therapeutic education with texts and photos on different
devices used with GH therapy, videos of a nurse carrying out a patient’s education with
demonstration of an injection, and lastly patients testimonies.

Module 3: “GH therapy or not? Benefits and long term risks.”
This module will explain the long term consequences of untreated GHD on cardio-vascular
risk, osteoporosis, body composition, muscular strength, all risks that are also raised by
cancer therapy received in childhood. Then it will explain the effects of GH therapy in
preventing these risks and the appropriate follow-up. For these aims, patients testimonies
and a video showing the first medical consultation after GH therapy start with
questions/answers should be a good option. Lastly, it will show what is known today on the
long term risks of GH therapy in the irradiated patient.

Module 4: “Why should I continue GH therapy given that I have stopped growing?”
This module is dedicated to adolescents in order to explain the effects of GH therapy other
than growth. It will repeat some items from the module 3 but in a way and language that
should be more attractive for adolescents (musical, BD, serious game…). A serious game is
one of our preferred solutions because it can convey a message to the player in an attractive
and fun way.

c) Forum

A forum will be available only for registered users of the MOOC. It will be moderated by a
community manager who will be our junior endocrinologist. Every patient or GP
participating to the MOOC can ask a medical question on post radiation pituitary sequelae,
get general or individual information on medical care or who needs an endocrine evaluation
or find a referent in his area.

d) Evaluation

The project manager will count every month the number of visits on our webpage and verify
that the keywords are well referenced on Google. He will count the number of registrations
on our MOOC.
The evaluation form will be based on analysis of the quiz. The quotation will be easy as the
same true/false questions will be asked before and after each module, allowing a scoring of
acquired knowledge for each module and each participant. As each module of the MOOC is
independent, we will be able to score which module was the best appreciated, which of
them was the most educational….

e) Innovation

Nowadays there is no educational website dealing with endocrine sequelae in survivors of
childhood cancer in France. We made a Google search with different key words in French
and we did not find any link. We then explored different French websites dealing with late
effects after childhood cancer and the only data that we found were those written by us.
We also looked for a special educational program on GH therapy on the web. The only website providing large information on GH treatment in French is that of EliLilly. To our knowledge, based on our responsibilities in the French Endocrine Society, in the French Pediatric Endocrine Society and in the French Society for Childhood Oncology and based on our contacts with patient’s associations, we are not aware of such a program in French, particularly dedicated to French-speaking patients.

5) Evaluation Design

a) **Main evaluation criteria:** Feasibility, use of the website and MOOC on post-radiation pituitary sequelae.

The satisfaction with the content, usability and design of the website for the patients will be studied by a specific questionnaire completed at the end of the training with the MOOC. The number of website visits will be counted by the project manager as well as the number of registrations to the MOOC (number of patients and GPs registrations) and the evolution in numbers followed up over time.

b) **Secondary evaluation criteria:**

**Improvement in the rate of survivors who restart endocrine follow-up, who remain on GH therapy at adult age or who restart GH therapy at adult age.**

To evaluate this criteria, every patient who will have participated in the MOOC will receive by email 6 and 12 months after their participation, a specific questionnaire that will be elaborated with the Inserm epidemiology team in order to know if:

- they have intended to start or restart endocrine follow-up
- they have actually started or restarted this follow-up
- a new endocrine assessment has been done
- GH therapy has been restarted if they are qualified for this treatment
- A few clinical anonymous data will be recorded for statistical analysis.

The medical practitioners will receive a questionnaire to know if:

- They will advise their patients to undergo endocrine assessment
- They will advise their patient to use GH therapy if qualified
- They actually did it and in how many patients
- If yes, did the patients follow their advice and how many of their patients started GH therapy?

A few clinical anonymous data on their patients will be recorded for statistical analysis.

For this part of this study we have planned to ask for prior agreement from our ethical board, if we get the funding. The preparation of this administrative file will be conducted together with the MOOC production so that the project can begin without delay as soon as the funding has been obtained.

Statistical analysis of the answers will be conducted by the epidemiology team, in terms of total numbers and percentage. If the numbers of answers allow it, the potential association with the following characteristics will be investigated: age, gender, cancer diagnosis, institutionalized individuals, educational levels and other associated medical conditions. Continuous variables will be tested with t-test ans categorical variables with Chi-square. We
will use non-parametric methods if necessary (Fisher’s test for categorical variables and Wilcoxon test for continuous variables).

Our objective is to increase by at least 20% the number of adult patients survivors of childhood cancer evaluated in our Endocrinology clinic (or another if the patient does not live in Ile de France area and prefers to be followed somewhere else).

**Improvement in the quality of care during transition period to allow absence of follow-up loss.**
This item will be analysed in the same manner as the previous one but limited to the number of adolescents who will follow the course.
Our objective is to decrease by 20% the number of patients lost to follow-up during transition.

**Perceived improvement in knowledge about childhood cancer late endocrine effects in survivors and medical practitioners.**
This point will be addressed by the analysis of the difference in the quiz answers before and after the specific training with the MOOC. A numeric scoring for each patient/GP will be defined by the number of true answers after the MOOC lowered by the number of true answers before the MOOC.

\[ c) \text{ Dissemination of the results} \]

The results on the efficiency of this approach in terms of improved medical management of these patients will be broadly disseminated by scientific communications during meetings on endocrinology and/or late effects after childhood cancer, by communications in meetings of patients associations and by a scientific paper.

**6) Detailed Workplan and Deliverables Schedule:**

This project is intended to start as soon as the funding will be available. We anticipated that we will get the funds in November 2017. If it will be later on, then the deliverables schedule should be delayed.
- **Start** in November 2017, end in December 2019.
- **Webpage Creation**: needs our webmaster help and to write the medical content of the pages. Last quarter of 2017.
- **MOOC design phase**: needs to write the medical content and the quiz, think of the several possible ways for best approaches, select service provider that offers the best service for our needs, create the MOOC and put it on line with the creation of the associated forum. First semester of 2018.
- **Obtaining institutional review board (IRB) and independent ethics committee (IEC) approval.** Registration with the French Data protection registrar in order to save email adresses in a computed file and send questionnaires to the MOOC participant afterwards. Last quarter 2017 and first semester 2018.
- **The MOOC and the associated forum will run** for 6 months: second semester of 2018.
- **Analysis of the results** of the MOOC associated quiz in terms of improvement of patients and GPs knowledge: first quarter of 2019.
- **Dissemination of the results** on knowledge improvement: second quarter of 2019.
- **Mailing of the questionnaires on efficiency** of the MOOC to improve medical care of patients: year 2019.
- **Analysis of the results of the questionnaires** on efficiency of the MOOC to improve medical care of patients: last quarter of 2019.
- **Dissemination of the results** on the efficacy on medical care: last quarter of 2019.

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E) **References**


2017-ong Leader of the HCP Bicêtre for Endo-ERN approved in 2017 (UE program for Rare Diseases Networks)
2005-ong. Basic research (renal effects of GH & AIP and pituitary tumorigenesis) at the lab of INSERM U1185 (Le Kremlin-Bicêtre)
2006-ong, Participation to Ercusyn (European Register on Cushing's Syndrome) (Programme of community action in the field of public health -2003-2008-)
2011 French expert for the International Consensus meeting “GH and IGF-I Assays, Present and Future” held in Charlottesville (North Carolina, USA)
2015 French expert for the international consensus meeting « Long-Acting GH » held in Asilomar (California, USA)
Since 2005, 70 invitations for international conferences and 38 invitations for national conferences

Publications:
249 Original Papers (80 during the last 5 years);
43 Review Papers & 60 Book Chapters (since 2000)
h-index : 55