COLLEGE OF MEDICINE AND HEATH SCIENCES

SCHOOL OF MEDICINE AND PHARMARCY

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

Determinants of Gestational Trophoblastic Neoplasia in Rwanda Retrospective Cohort Study

Dissertation Submitted in Partial Fulfillment of the Requirements for the Award of Degree of Master of Medicine in Obstetrics and Gynecology of the University Of Rwanda

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KIGALI, AUGUST 2021

Declaration

The researcher:

I hereby declare that this dissertation **"*Determinants of Gestational Trophoblastic Neoplasia in Rwanda Retrospective Cohort Study*"** is my own work and it has not been submitted by any other university for the award of a degree.

Signed

Date 31/08/2021

Dr Magnifique Irakoze

The supervisor:

I hereby declare that this dissertation **"*Determinants of Gestational Trophoblastic Neoplasia in Rwanda Retrospective Cohort Study*"** was submitted by Dr Magnifique Irakoze.

Signed

Date 31/08/2021

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DEDICATION

To the Almighty God who cares about us,

To my late Father Ngabo John, my lovely mother Sophie Nyiranzaninka, I owe my success,

To the love of my life, My Fiancée Dr Sarah Elizabeth Podwika,

To my siblings Daniel, Edison, Albert and Ange,

I dedicate this work.

ACKNOWLEDGEMENT

I am very grateful to the Almighty God who has held my hands and led my steps throughout this program.

This work would not have been realized without the intervention of many people to whom I address my deep gratitude.

To all academic and administrative authorities of the University of Rwanda (UR), College of Medicine and Health Sciences, Faculty of Medicine and Pharmacy for a high quality of education. My gratitude goes also to my lecturers and mentors, for their involvement during my training.

My acknowledgements to Dr. Diomede NTASUMBUYANGE who has agreed to supervise This work. His guidance, devotion and considerable inputs have been of a great importance to the achievement of this work. I was blessed and privileged to train and grow under him.

To Dr Lisa BAZETT MATABELE who started the Gestational Trophoblastic Neoplasia registry at the Kigali University Teaching Hospital I extend my gratitude.

Finally, I would like to thank to my classmates and all OB/GYN residents, who have been helpful and made this journey possible with their daily encouragement.

LIST OF ABBREVIATIONS

β-HCG: Beta Human Chorionic Gonadotropin

CCH; Choriocarcinoma

CHM: Complete Hydatidiform Mole

CHUK: Centre Hospitalier Universitaire de Kigali

ETT: Epithelioid Trophoblastic Tumor

FIGO: Fédération Internatianale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics)

GTD: Gestational Trophoblastic Disease

GTN: Gestational Trophoblastic Neoplasia

IM: Invasive Mole

PSTT: Placenta Site Trophoblastic Tumor

SPSS: Statistical Package for the Social Sciences

WHO: World Health Organization

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ABSTRACT:

Background: Gestational trophoblastic neoplasia (GTN) is rare disease affecting reproductive age women. It includes a spectrum of malignant neoplasms due to abnormal development of trophoblastic tissues of the plaenta. GTN in Rwanda is not well studied. The aim of this study was to determine patient and disease characteristics of the women with GTN who were followed at a major university hospital in Kigali Rwanda.

Methods: This was retrospective cohort study of women diagnosed with GTN at Kigali University Teaching Hospital (CHUK) between July 2015 and July 2020. Data were extracted from the GTN Database, a disease registry, with additional data retrieved from the patient file as needed. Information collected included: nationality, residence, maternal age, gestational event leading to GTN, pathologic diagnosis if available, FIGO stage and WHO score, number of chemotherapy cycles completed and clinical outcome. Descriptive statistics were calculated for all variables. Chi square and Exact Fisher test were used for measure of association and a P value of <0.05 was considered significant.

Results: The majority of patients were diagnosed with low-risk disease (78.4%). The most common type of GTN was post-molar (86.5%) and 67.6% of women had disease confined to the uterus. Hysterectomy was performed for 40 (54%) women as part of their management for GTN. Patients who underwent hysterectomy, compared to those with a preserved uterus, had shorter treatment duration median (45 days vs 115 days) and received fewer chemotherapy cycles (median 2 cycle's vs 4.5 cycles). The cure rate among patient followed at CHUK was 84.8% and 9.1% failed single agent chemotherapy with referral for additional chemotherapy and 6.1% died.

Conclusion: The majority of GTN patients treated CHUK successfully achieved remission at the rate of 84.8 %. However, one third of all patients with GTN in this study had an undocumented outcome; there is an opportunity to improve documentation and patient surveillance. There is a need for an innovative follow up plan, especially post hysterectomy.

Keyword: gestational trophoblastic neoplasia, metastasis, hysterectomy, number of cycles

INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a spectrum of pregnancy-related disorders that develop from the placenta.[1] The World Health Organization classifies GTD into premalignant disease, including complete and partial hydatidform mole (molar pregnancies), and a malignant condition known as gestational trophoblastic neoplasia (GTN).[2] GTN includes choriocarcinoma, invasive mole, placental-site trophoblastic tumour, and epithelioid trophoblastic tumour.[3] Furthermore, if after evacuation of a molar pregnancy there are four values or more indicating an BHCG plateau for 3 weeks, a rise of BHCG of 10% for three values during a period of at least 2 weeks, or persistence of BHCG six months after evacuation, it meets the criteria for a type of GTN known as persistent hydatidiform mole[1]. Treatment of GTN involves chemotherapy and possible surgery[2]. Both single agent (methotrexate) and multi-agent chemotherapy regimens are used, depending on the severity of the disease[4]. The World Health Organization has developed a classification system to help guide treatment decisions[5]. This scoring system is used in Rwanda and globally.

The burden of GTN varies significantly accross regions of the world[6]. The highest frequencies are reported in Asia, with Indonesia leading with an incidence is 10 cases per 1000 pregnancies[7]. The etiology of GTN is not fully understood. Risk factors of GTD, which usually precede GTN, have been well documented and include history of molar pregnancy, extreme maternal age, parity, race, nutrition, ABO blood types, prior cesarean delivery, cytogenetics of the molar pregnancy and socio-economic status of both patient and the country.[7]

Very few studies on GTD have been conducted in Rwanda. The incidence of 1.5 cases of GTD per 1000 pregnancies has been reported at the University Teaching Hospital of Kigali (CHUK).[8] A study conducted in Rwanda at the Butaro Cancer Center of Excellence reported on management of GTN, treatment outcomes, and factors associated with the potential for improved outcomes among patients with GTN.[9] However, data assessing determinants of GTN among women in reproductive age in Rwanda are still lacking. Therefore, the aim of this study was to elucidate determinants which contributed to the development of GTN in Rwandese women who were treated at CHUK. Additionally, patient characteristics and outcomes, including management, via surgery and/or single agent or multi agent chemotherapy, and patient follow up were assessed.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at CHUK for women diagnosed with GTN between July 2015 and July 2020. Data were extracted from the GTN Database maintained by CHUK. GTN patients were referred to CHUK for evaluation and to initiate single agent chemotherapy regimen. Patients requiring multi-agent chemotherapy were then referred to Butaro Cancer Center. By total enumerative sampling we included 74 GTN patients who consulted and were treated at CHUK during July 2015 to July 2020. Patients were excluded if they had initially been admitted for GTN and later diagnosed with a different pathology. When needed, the patient files were retrieved and reviewed to complete missing data. A questionnaire was used to record nationality, residence, maternal age, gestational event leading to GTN, pathologic diagnosis if available, FIGO stage and WHO score, number of chemotherapy cycles completed and clinical outcome.

Data were exported to SPSS version 22.0 then cleaned and analyzed. Descriptive statistics were calculated for all variables. Chi square and Exact Fisher test were used for measure of association and a P value of <0.05 was considered significant. If data was missing for a variable, it was assumed to be randomly missing, and thus the missing completely at random mechanism was applied. Hence, complete-case analysis was applicable. The study was approved by both the institution review board of the University of Rwanda and Kigali University Teaching Hospital.

RESULTS

Seventy-four patients with GTN consulted and were treated at CHUK over a period of 5 years from July 2015 to July 2020. All of these women were part of the GTN Database, a disease registry established at CHUK by a Gynecologist Oncologist. All of the women were of East African descent. The mean age of study participants was 37 years; age range of 20 – 56 years, with 39 (52.7%) of the study participants under 40 years old and 35(47.3%) age 40 or over. Twenty women (27%) were residents of Kigali and the remaining women 54 (73%) were from outside providences. Regarding the pregnancy outcome preceding the GTN diagnosis, sixty-four (86.5%) had a molar pregnancy as the antecedent, 8 women (12.9%) had term pregnancy, and 2 (3.2%) had abortion (Table 1). Thirty-one women (41.9%) had histopathology results to confirm their diagnosis, while

for the remainder, a diagnosis of GTN was established based on clinical, imaging and quantitative BHCG results (Table 2).

Based on WHO GTN Risk score, 58 patients (78.3%) had a low risk GTN while 16 women (22.9%) had high risk GTN (Table2). Patients with low risk GTN were treated with 5 days of intramuscular (IM) methotrexate (0.4mg/kg/day, maximum dose 25mg/day). The 16 patients with high risk GTN at initial consultation at CHUK were referred at Butaro Cancer Center for multi-agent chemotherapy (Table 2).

There were no metastases in 50 (67.6%) of women, classified as FIGO Stage I GTN. The remaining 24 women (32.4%) had metastatic disease. For the patients with metastatic disease, 7 (9.5%) were diagnosed with FIGO stage II disease, 16 (21.6%) were diagnosed with stage III disease, and 1 (1.3%) had stage IV disease. The most common pathology for GTN patients was invasive mole found in 63 (85.1%) cases followed by choriocarcinoma in 10 (13.5%) of patients. There was also one (1.3%) case of placental site trophoblastic tumor, confirmed by histopathology. Treatment was single agent methotrexate chemotherapy in 58 (78.3%) of women and 16 (23%) were referred for multi-agent chemotherapy. Hysterectomy was performed as part of treatment in 40 (54%) of women in this study. (Table 2)

The women who underwent hysterectomy as part of their treatment had a median of 2 cycles of single agent chemotherapy, with a range of 1-13 cycles, compared to a median of 4.5 cycles with a range of 1-14 cycles for patients with a preserved uterus. The median duration of follow up was 45 days for patients who had a hysterectomy compared to a median of 115 days in those with the uterus preserved (Table3). Patients were considered to be lost to follow up when they failed to attend their appointments before reaching three negative beta-HCG levels.

We found that in women who underwent hysterectomy and were treated with single agent chemotherapy, 1 (2.5%) failed single agent therapy and was subsequently referred for multi-agent chemotherapy, 10 (25%) were referred for multi-agent chemotherapy post-operatively due to high risk disease, 16 (40%) their treatment outcome was not documented and 2 (2.7%) died from GTN before initiation of chemotherapy (Table 4). In the group of women whose uterus was preserved, 2 (5.8%) failed single agent therapy and were referred for multi-agent chemotherapy, 5 (12.7%) were referred for multi-agent chemotherapy due to high risk disease, 9

(26.4%) their treatment outcome was not documented and 1 (2.9%) died during treatment. (Table 4) Among the patients with preserved uterus, 18 women (52.9%) chose levonogestrel-releasing implant as the contraception of choice.

Unfortunately, not all women had complete documentation regarding their treatment and outcomes. Only 49 of 74 women had complete documentation in their chart. Of these women with complete documentation 16 (22.9%) were transferred to Butaro Cancer Center immediately for multi-agent chemotherapy. Of those treated with single agent therapy at CHUK, 28 (84.8%) were cured and achieved complete remission, 3 (9.1%) failed single agent chemotherapy and were subsequently referred to Butaro Cancer Center, and 2 (6.1%) died before transfer. (Figure 1)

DISCUSSION

The aim of this study was to characterize women with GTN at CHUK and evaluate maternal outcomes associated with the disease. In our study the mean patient age was 37 years and 47% of the women were above 40 years of age. Women in our study were older than women in a study performed in Thailand where the mean age was 33 years with 24.3% above 40 years.[10] An additional study performed in Lagos, Nigeria had an age range of 21-30 years for women affected by GTN.[11] The older age of patients in our study could explain the higher hysterectomy rate for treatment of GTN in our study population.

Our results showed that GTN followed a molar pregnancy in 86.5% of women. These findings are similar to those in Thailand where molar pregnancy preceded 84% of cases of GTN and in Egypt where 83% of GTN cases were preceded by a molar pregnancy.[12] Our results also confirmed prior study results in Rwanda from Butaro Cancer Center that GTN arising from GTD in the Rwandan population is much higher than following other pregnancy outcomes.[9,12]

Our patients were geographically distributed in all 4 provinces of Rwanda, with 73% living outside of Kigali. This geographic distribution could have affected the high number of undocumented outcomes.

Our findings showed that for women who underwent hysterectomy (54%) the surgery was associated with shorter treatment duration and fewer chemotherapy cycles. This is similar to a study performed in India which showed that patients who had a hysterectomy experienced a shorter time to achieve remission and fewer chemotherapy cycles[13].

In our study, 78.4% of the patients had low risk GTN. This is consistent with study results in Senegal where 88.4% of women presented with low risk disease and were treated with single agent chemotherapy.[14] In our patient population 67.6% of GTN patients presented without metastatic disease. For those women with metastases, the lungs were the most common site of spread, found in 21.6% of women. This is supported by previous studies .[1516]

It is important after a GTD/ GTN diagnosis to have reliable contraception, and for the women who did not have a hysterectomy, 52.9% had long-acting reversible contraception in the form of a levonogestrel implant. GTN/GTD patients are advised to refrain from pregnancy while on treatment[4].

For the women in our study, with completed documentation who received all of their treatment at CHUK, there was a high cure rate of 84.8%. Similar to the study done in Bangkok Thailand where the GTN cure rate was 83.8%.[12] The burden in management and follow up of GTN in this study was undocumented outcome, defined as patient with no record of three negatives in the GTN database or electronic medical record at CHUK. Undocumented outcome particularly affected the post-hysterectomy group 16 (40%). A study performed in Australia and New Zealand on GTD found 14.9% of patients had loss of follow up. In the study, some patients chose to consult their family physician and others were lost follow up for undocumented reasons[17]. Despite counseling on the need for adjuvant chemotherapy after hysterectomy, some patients may have considered hysterectomy as a definitive management of GTN and therefore abandoned the follow up. The high number of undocumented outcome rate may also be due to the long-distance patients had to travel, with 73% of our women living outside Kigali with an average distance of one hundred kilometers from CHUK. Thus, counseling remains an important part of the management plan since it is known that despite shortening the duration and number cycles of chemotherapy, hysterectomy alone is not adequate for cure of GTN.

Chemotherapy is always recommended even when hysterectomy has been completed and thus the importance of adherence to a follow plan should be stressed.[18]

STRENGTHS and LIMITATIONS

The strength of this study was the number of GTN cases when compared to other studies in Rwanda.[8,9] This large sample size is likely due to the specialized treatment by a gynecologic oncologist at CHUK; patients from throughout Rwanda and neighboring countries were referred to and treated at our facility due to this specialized care. Additionally, our study is the first of the kind for the region as there are no available published studies on GTN studies that assessed both risk factors and treatment outcomes in the region.

A limitation of our study is that it did not assess other determinants know to be associated with GTN such as ABO blood type, multiparty and vitamin A deficiency.[19,20] Additionally, the information for the high risk patients who were referred to Butaro Cancer Center for multi-agent chemotherapy and their assessment of follow up and outcomes post treatment was limited.

CONCLUSION

Although GTN is a rare disease, our study shows that low risk GTN types are effectively managed at CHUK with 84.8 % of women achieving complete remission on single agent chemotherapy. However, given that one third of all patients with GTN in this study had an undocumented outcome, there is a need for an innovative follow up plan that addresses the causes of drop out. This includes both provider and patient education with emphasis on the importance of follow up and discussion of persistent or recurrent disease. Having local district hospitals follow B-HCG levels with the ability to transmit results to a centralized teaching institution, could save patients time and money on travel. The COVID-19 pandemic forced some strict measures on personal mobility including patients who were not severely ill, resulting in patients missing appointments and a considerable number lost to follow up.

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APPENDIX:

TABLE 1: DEMOGRAPHICS

Demographic		Frequency (%) N=74
Residence	Kigali City	20(27%)
	Southern Province	20(27%)
	Northern Province	15(20.3%)
	Eastern Province	11(14.9%)
	Western Province	8(10.8%)
Age Group	<40	39(52.7%)
	≥40	35(47.3%)
Mean Age	37.7 +- 10.6 range (20-56)	
Antecedent pregnancy	Molar Pregnancy	64(86.5%)
	Term pregnancy	8(12.9%)
	Abortion	2(3.2%)

TABLE 2: GTN PROFILE

GTN Characteristics		Frequency (%) N=74
Diagnosis	Clinical (B-HCG, U/S)	43(58.1%)
	Pathological	31(41.9%)
WHO GTN Risk score	≤6 (Low Risk GTN)	58(78.3%)
	> 6 (High Risk GTN)	17(22.9%)
FIGO GTN Stage	Stage I	50(67.6%)
	Stage II	7(9.5%)
	Stage III	16(21.6%)
	Stage IV	1 (1.3%)
Type of GTN	Invasive mole	63(85.1%)
	Choriocarcinoma	10(13.5%)
	Placental site trophoblastic tumor	1(1.4%)
Chemotherapy treatment	Methotrexate at CHUK	58(78.3%)
	Referred to BUTARO for EMACO	16(22.9%)
Contraception	Medroxyprogesterone acetate	2(2.7%)
	Levonogestrel implant	18(24.3%)
	Levonogestrel Ethinylestradiol	2(2.7%)
	Hysterectomy	40(54.1%)
	Declined contraception	2(2.7%)
	Not documented	10(13.5%)
Site of Metastasis	None	50(67.6%)
	Vagina	11(14.9%)

Lungs	16(21.6%)
Brain	1(1.4%)

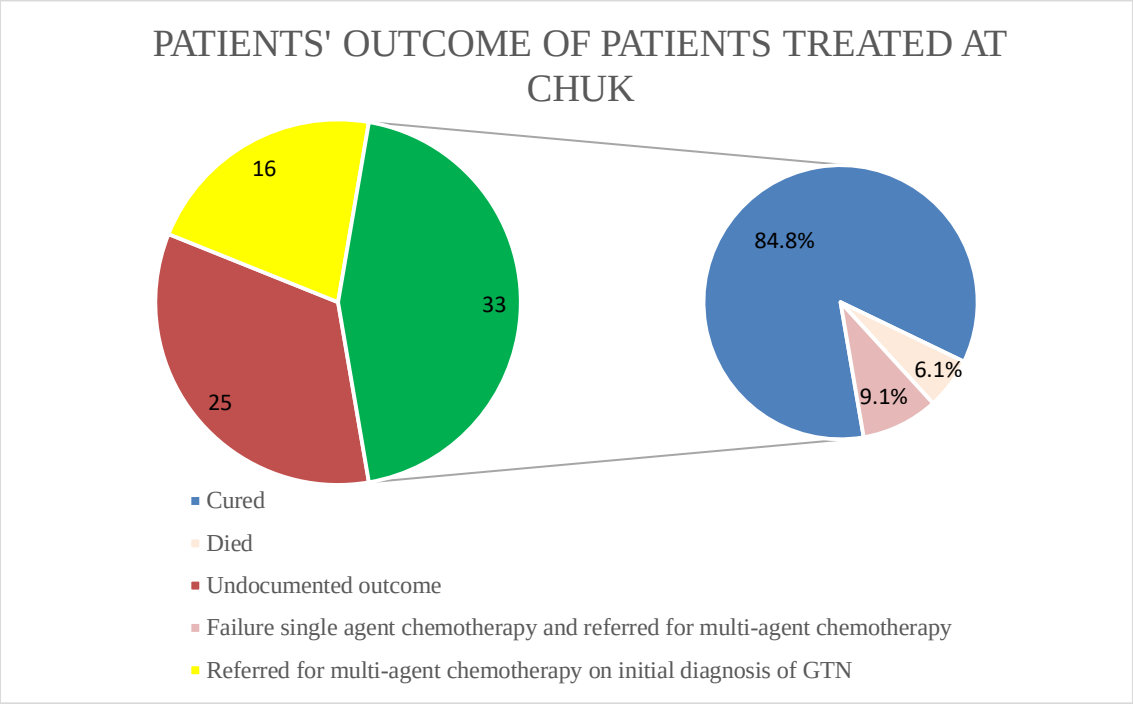
TABLE 3: INFLUENCE OF HYSTERECTOMY ON NUMBER OF CYCLES AND DURATION OF FOLLOW UP OF PATIENTS WITH GTN

Status of the uterus:		Preserved Uterus	Hysterectomy Completed
Cycles of Chemotherapy (number of cycles)	N	28	39
	Mean	4.96	3.46
	Std. Deviation	+/- 4.3	+/- 3.6
	Median	4.5	2.0
Duration of follow up (in days)	N	21	23
	Mean	112.29	78.61
	Std. Deviation	+/- 71.89	+/- 77.43
	Median	115.00	45.00

TABLE 4: COMPARISON OF PATIENTS WITH GTN WHO UNDERWENT HYSTERECTOMY AND THOSE WITH A PRESERVED UTERUS

Patient Outcomes	Patients status post Hysterectomy N= 40	Patients with a preserved uterus N = 34	P-Value
Failed single agent and referred for multi-agent chemotherapy	1(33.3%)	2(66.7%)	0.863
Undocumented Outcome	16 (64%)	9 (36%)	0.071
Referred for multi-agent chemotherapy	11 (66.7%)	6 (35.2%)	0.087
Died	2(100%)	0(0%)	0.367

FIGURE 1: PATIENT OUTCOME



UNIVERSITY of RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

DIRECTORATE OF RESEARCH & INNOVATION

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 29th /July /2021

Dr. IRAKOZE Magnifique
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 258/CMHS IRB/2021

Your Project Title ***"Determinants of Gestational trophoblastic Neoplasia in Rwanda: Retrospective cohort study"*** has been evaluated by CMHS Institutional Review Board.

Name of Members	Institute	Involved in the decision		
		Yes	No (Reason)	
			Absent	Withdrawn from the proceeding
Prof Kato J. Njunwa	UR-CMHS	X		
Dr Stefan Jansen	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS		X	
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 23rd July 2021, **Approval has been granted to your study.**

Please note that approval of the protocol and consent form is valid for **12 months**.

Email: researchcenter@ur.ac.rw P.O Box 3286 Kigali, Rwanda www.ur.ac.rw

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 29th July 2021

Expiration date: The 29th July 2022

Dr. Stefan Jansen
Ag. Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:
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CENTRE HOSPITALIER UNIVERSITAIRE
UNIVERSITY TEACHING HOSPITAL

Quality Health Care Training & Research

Ethics Committee / Comité d'éthique

18th Aug,2021 *Ref.:EC/CHUK/091/2021*

Review Approval Notice

Dear Magnifique Irakoze,

*Your research project: "**Determinants of gestational trophoblastic neoplasia in Rwanda: retrospective cohort study.** "*

During the meeting of the Ethics Committee of University Teaching Hospital of Kigali (CHUK) that was held on 18th Aug,2021 to evaluate your request for ethical approval of the above mentioned research project, we are pleased to inform you that the Ethics Committee/CHUK has approved your research project.

You are required to present the results of your study to CHUK Ethics Committee before publication by using this link:www.chuk.rw/research/fullreport/?appid=420&&chuk.

PS: Please note that the present approval is valid for 12 months.

Yours sincerely,

Dr Emmanuel Rusingiza Kamanzi
The Chairperson, Ethics Committee,
University Teaching Hospital of Kigali

ETHICS COMMITTEE
CHUK

Scan code to verify.

" University teaching hospital of Kigali Ethics committee operates according to standard operating procedures (Sops) which are updated on an annual basis and in compliance with GCP and Ethics guidelines and regulations "