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Gynaecologic Oncology Society of Kenya (GOSK) clinical management protocol for gestational trophoblastic neoplasia (GTN) in Kenya - 2026

Gideon M. Mutua[1,2*], Innocent O. Maranga[1,2,3], Yusuph Mwidibo[1,2], Naomi N. Sitati[1,2], Anwar Z. Mohamed[1,2], Stella N. Njenga[1,2], Diana Marion[1,2], Simon M. Gitau[1,2], Steven M. Ibua[1,2], Bruce O. Semo[1,2,4], Isaac M. Maingi[1,2], Victor T. Otieno[1,2], Francis O. Abinya[1,2], Margaret Kilonzo[1,2], Eunice Cheserem[1,2], Alfred Mokomba[1,2], Wycliffe Musalia[1,2], Millicent Masinde[1,2], Benjamin E. Odongo[4], Jacqueline Chesang'[5], Victor T. Otieno[1,2], Rose J. Kosgei[1,2]

[1]Department of Obstetrics and Gynecology, University of Nairobi, Nairobi, Kenya
[2]Department of Obstetrics and Gynecology, Kenyatta National Hospital, Nairobi, Kenya
[3]School of Medical Sciences, Amref International University, Nairobi, Kenya
[4]Department of Obstetrics and Gynecology, Kenyatta University, Nairobi, Kenya
[5]Department of Public and Global Health, University of Nairobi, Nairobi, Kenya

***Correspondence:** gideonmut@gmail.com

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Abstract

Objective: To establish a standardized, evidence-based approach to the management of gestational trophoblastic neoplasia (GTN) in Kenya.

Methods: This protocol was developed using a guideline adaptation approach, drawing on high-quality international clinical practice guidelines and contextualizing their recommendations to Kenya's health care system and available resources. A multidisciplinary panel comprising gynecologic oncologists, pathologists, radiologists, oncology nurses, pharmacists, radiation oncologists, public health specialists, and patient representatives contributed to the process. Panel members received technical training from experts at the University of Nairobi and Kenyatta National Hospital on evidence-based guideline adaptation, including standardized appraisal, systematic evaluation of guidelines, and contextualization to local needs. A systematic literature search was conducted in PubMed and Google Scholar. Six guidelines were identified and independently appraised using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. Four guidelines were selected for adaptation: the National Comprehensive Cancer Network (NCCN) Guidelines for Gestational Trophoblastic Neoplasia (2025); the International Federation of Gynecology and Obstetrics (FIGO) 2021 update on the diagnosis and management of gestational trophoblastic disease; the European Organization for Treatment of Trophoblastic Diseases (EOTTD) Practical Clinical Guidelines for Treatment and Referral of Gestational Trophoblastic Disease (2020); and the Society of Obstetricians and Gynaecologists of Canada (SOGC) Guideline No. 408: Management of Gestational Trophoblastic Diseases (2021). Recommendations from these guidelines were reviewed and contextualized to Kenya's health care infrastructure and resource setting.

Results: The protocol provides recommendations for the diagnosis, risk stratification, treatment, and follow-up of GTN. Diagnosis is based on the FIGO criteria, while the WHO-modified scoring system is used to classify patients into low-risk and high-risk categories. The protocol also identifies an ultra-high-risk group requiring specific treatment considerations. Single-agent chemotherapy is recommended for appropriately selected patients with low-risk GTN, whereas multi-agent chemotherapy is recommended for high-risk and ultra-high-risk disease. Surgery is a principal component of management for placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). The protocol also addresses the management of recurrent disease, post-treatment surveillance, fertility and reproductive health considerations, and supportive and palliative care.

Recommendations: This protocol provides a standardized framework for the evidence-informed management of GTN in Kenya. It is intended to support consistent clinical decision-making, multidisciplinary care, appropriate use of available resources, and improved patient outcomes.

Keywords: Gestational trophoblastic neoplasia; Gestational trophoblastic disease; Hydatidiform mole; Kenya

List of abbreviations

AGREE II	Appraisal of Guidelines for Research and Evaluation II
BEP	Bleomycin, etoposide, and cisplatin
CBC	Complete blood count
CNS	Central nervous system
CT	Computed tomography
EOTTD	European Organization for Treatment of Trophoblastic Diseases
ETT	Epithelioid trophoblastic tumor
EMA-CO	Etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine
EMA-EP	Etoposide, methotrexate, actinomycin D, etoposide, and cisplatin
EP-EMA	Etoposide, cisplatin, etoposide, methotrexate, and actinomycin D
FIGO	International Federation of Gynecology and Obstetrics
G-CSF	Granulocyte colony-stimulating factor
GOSK	Gynaecologic Oncology Society of Kenya
GTD	Gestational trophoblastic disease
GTN	Gestational trophoblastic neoplasia
hCG	Human chorionic gonadotropin
ICE	Ifosfamide, carboplatin, and etoposide
IM	Intramuscular
IV	Intravenous
LFTs	Liver function tests
MEC	Medical Eligibility Criteria
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PO	By mouth (oral administration)
PSTT	Placental site trophoblastic tumor
RFTs	Renal function tests
SC	Subcutaneous
SOGC	Society of Obstetricians and Gynaecologists of Canada
TIP	Paclitaxel, ifosfamide, and cisplatin
TP/TE	Paclitaxel–cisplatin/paclitaxel–etoposide
VIP	Etoposide, ifosfamide, and cisplatin
WHO	World Health Organization

Summary of GOSK recommendations

This protocol provides evidence-informed recommendations for the diagnosis, risk stratification, treatment, and follow-up of patients with gestational trophoblastic neoplasia (GTN) in Kenya. It is intended for gynecologic oncologists, medical oncologists, gynecologists, pathologists, radiologists, oncology nurses, pharmacists, and other health care professionals involved in the care of patients with GTN across different levels of the health care system. The recommendations address diagnostic evaluation; first- and second-line management of low-risk and high-risk GTN; management of ultra-high-risk disease; treatment of placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT); special clinical considerations; post-treatment surveillance; supportive and palliative care; and recurrent disease.

The recommendations are summarized in Tables 1–9. Detailed explanations, supporting evidence, and treatment considerations are presented in the relevant sections of the protocol. Clinical decisions should be individualized according to disease characteristics, prior treatment, patient preferences, and the availability of appropriate services and resources.

Table 1. Summary of GOSK recommendations for the diagnostic evaluation of GTN

Domain	GOSK recommendations
History	Obtain a comprehensive history, including age, abnormal vaginal bleeding, cough, dyspnea, type of antecedent pregnancy (molar, miscarriage, term pregnancy), interval months from the end of the index pregnancy to treatment, and, if recently treated for GTN, whether there is previous failed chemotherapy.
Physical examination	Perform a comprehensive physical examination, including: 1. General examination to elicit possible anemia due to bleeding, and respiratory distress due to lung metastasis. 2. Pelvic examination with bimanual examination to evaluate uterine enlargement and the presence of bilateral adnexal masses due to theca-lutein cysts. Pelvic assessment is done with caution to avoid triggering massive hemorrhage in cases of vaginal metastases. 3. Speculum examination to assess for vulvar and vaginal metastases. 4. Examine the other systems to check for the presence of metastases.
HCG	Perform quantitative serum hCG testing for all patients with suspected GTN. In patients with prior molar pregnancy, serial hCG monitoring should be used during post-treatment surveillance. The FIGO Criteria for Diagnosis of Post-Molar Gestational Trophoblastic Neoplasia[1] *should be applied to make a diagnosis of GTN.*
Laboratory	Perform CBC, RFTs, and LFTs as baseline tests and to evaluate for possible metastases. Thyroid function tests should be performed in patients with serum beta-hCG> 100,000 mIU/ml.
Imaging	An abdominal and pelvic ultrasound is done to rule out a pregnancy and to check the adnexa and any liver metastases. A chest X-ray is initially performed; if metastases are suspected or identified, a contrast-enhanced CT scan of the chest, abdomen, and pelvis, as well as a contrast-enhanced brain MRI, are recommended. Imaging should report the presence of metastases, the site and number of metastases, the size of each metastasis, including the largest tumor size, and the size of the uterus (in centimeters).
Pathology	Obtaining a biopsy should generally be avoided because of the risk of severe hemorrhage. Histologic confirmation is not required for the diagnosis of GTN.

[1]FIGO Criteria for Diagnosis of Post-Molar Gestational Trophoblastic Neoplasia:

1. *Plateau of hCG levels (<10% change): Four measurements over a period of 3 weeks or longer (days 1,7,14, and 21).*
2. *Rising hCG levels (>10% change): Three consecutive weekly measurements over at least a period of 2 weeks or more (days 1,7, and 14).*
3. *Histologic diagnosis of choriocarcinoma.*

CBC: complete blood count; CT scan: computed tomography scan; FIGO: International Federation of Gynecology and Obstetrics; GOSK: Gynaecologic Oncology Society of Kenya; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; LFTS: liver function tests; MRI: magnetic resonance imaging; RFTS: renal function tests.

Table 2. Summary of GOSK recommendations for first-line management of low-risk GTN

Domain	GOSK recommendations
Criteria	There are two categories of low-risk GTN patients: category one, patients who require single-agent chemotherapy, and category two, patients who require multi-agent chemotherapy. • Category One In low-risk GTN, where the WHO score is 0-4, serum hCG is < 100,000 mIU/ml, there is no histological diagnosis of choriocarcinoma, and there is no evidence of metastases, the recommended first-line treatment is single-agent chemotherapy with methotrexate or actinomycin D. • Category Two In low-Risk GTN, where the WHO score is 5 or 6, serum hCG is >100,000 mIU/ml, or there is a confirmed histological diagnosis of choriocarcinoma, massive per vaginal bleeding, and metastases are present, the recommended first-line treatment is multi-agent chemotherapy (EMACO). Manage all patients with GTN through a multidisciplinary team
Chemotherapy	• Chemotherapy is administered until normalization of hCG (≤5 mIU/mL).

Domain	GOSK recommendations
	• Category One (Patients who require single agent chemotherapy) 1. Methotrexate 1 mg/kg IM on Days 1, 3, 5, and 7, alternating with folinic acid 15 mg orally on Days 2, 4, 6, and 8, every 2 weeks. OR 2. Methotrexate 0.4 mg/kg/day IV for 5 days, every 2 weeks. OR 3. Actinomycin D 0.5 mg IV for 5 days, every 2 weeks. OR 4. Actinomycin D pulse 1.25mg/m^2 IV, every 2 weeks (when hCG <3000 mIU/ml). • Category Two (Patients who require multi-agent chemotherapy) EMA-CO regimen (every two weeks) Etoposide 100mg/m^2 IV infusion (days 1 and 2) Actinomycin D 0.5mg IV bolus (days 1 and 2) Methotrexate 300 mg/m^2 IV infusion (day 1), Leucovorin 15 mg IM or PO q12 hours x 4 (days 2 and 3), Cyclophosphamide 600 mg/m^2 IV infusion (day 8) Vincristine (oncovin) 1 mg/m^2 IV bolus (day 8).
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. • Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	Perform clinical assessment and evaluate hCG levels, complete blood count, liver function tests, and renal function tests at the start of each treatment cycle.
Contraception	Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria.
Consolidation	• Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). ▪ For single-agent chemotherapy, administer two more cycles of consolidation chemotherapy. ▪ For multi-agent chemotherapy (EMA-CO), administer three more cycles of consolidation chemotherapy.
BEP: Bleomycin, Etoposide, Cisplatin; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D, GOSK: Gynaecologic Oncology Society of Kenya, GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria, TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Table 3. Summary of GOSK recommendations for second-line management of low-risk GTN

Domain	GOSK recommendations
Criteria	Patients with poor response to initial therapy, defined as: 1. hCG plateau (<10% change) over 3 treatment cycles. 2. hCG rise (>10% change) over 2 treatment cycles. 3. Refractory organ toxicity due to initial single-agent chemotherapy Manage all patients with GTN through a multidisciplinary team.
Chemotherapy	• Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). 1. EMACO is the preferred second-line regimen administered as indicated above in Table 2. 2. In poor response to EMA-CO, the recommended second-line chemotherapy regimen includes: EMA-EP or EP-EMA and platinum-based regimens (TP/TE, BEP, VIP, ICE). EMA-EP regimen (every two weeks) Etoposide 100 mg/m^2 IV infusion over 1 hour (day 1) Methotrexate 300 mg/m^2 IV infusion over 12 hours (day 1) Actinomycin D 0.5 mg IV bolus (day 1) Leucovorin 15 mg IM or PO q12 hours x 4 (days 2 and 3) Etoposide 100-150 mg/m^2 IV infusion over 1 hour (day 8) Cisplatin 75 mg/m^2 IV infusion over 2 hours (day 8) Granulocyte colony-stimulating factor support:5 mcg/kg SC (days 9-14) EMA-EP regimen (every two weeks) Etoposide 100–150 mg/m^2 IV over 1 hour (day 1) Cisplatin 75 mg/m^2 IV over 2 hours (day 1) Etoposide 100 mg/m2 IV over 1 hour (day 8) Methotrexate 300 mg/m^2 IV infusion over 12 hours (day 1) Leucovorin 15 mg PO (preferred) or IM every 12 hours for 4 doses beginning 24 hours after the start of the methotrexate infusion Actinomycin D 0.5 mg IV push (day 1) Granulocyte colony-stimulating factor support:5 mcg/kg SC (days 3-6 and 10-13).
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions.

Domain	GOSK recommendations
	• Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. Review complete blood count, liver function tests, and renal function tests.
Contraception	Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria.
Consolidation	• Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). • Administer three cycles of consolidation chemotherapy.
BEP: Bleomycin, Etoposide, Cisplatin; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D, GOSK: Gynaecologic Oncology Society of Kenya, GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria, TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Table 4. Summary of GOSK recommendations for first-line management of high-risk GTN

Domain	GOSK recommendations
Criteria	• Involve a multidisciplinary team (MDT) in the management of High-Risk GTN • Recommended criteria for first-line management for High-Risk GTN: 1. FIGO score 7-12 2. Stage IV disease
Chemotherapy	• Chemotherapy is administered until normalization of hCG result (≤5 mIU/mL). Administer EMA-CO as the preferred first-line chemotherapy regimen (see Table 2 above for dosages).
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. • Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle, and perform complete blood count, liver function tests, and renal function tests.
Contraception	Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria.
Consolidation	• Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). • Administer three cycles of consolidation chemotherapy.
EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; GOSK: Gynaecologic Oncology Society of Kenya; GTN: Gestational Trophoblastic Neoplasia, hCG: human chorionic gonadotropin; MEC: Medical Eligibility Criteria; WHO: World Health Organization.	

Table 5. Summary of GOSK recommendations for second-line management of high-risk GTN

Domain	GOSK recommendations
Criteria	• Involve a multidisciplinary team (MDT) in the management of High-Risk GTN • Recommended criteria for second-line treatment for High-Risk GTN: 1. Incomplete response to EMA-CO, defined as a plateau or rise in hCG levels. 2. Stage IV disease with initial response to EMA-CO followed by hCG plateau or incomplete response to treatment.
Chemotherapy	Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). 1. EMA-EP or EP-EMA (see dosages in Table 3 above). 2. Alternative regimens for patients who are intolerant to EMA-EP: platinum-based regimens (TP/TE, VIP, ICE, BEP) and immunotherapy (pembrolizumab)
Treatment monitoring	Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. Review complete blood count, liver function tests, and renal function tests.
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. • Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Contraception	Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria.
Consolidation	• Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). • Administer three cycles of consolidation chemotherapy.

Domain	GOSK recommendations
BEP: Bleomycin, Etoposide, Cisplatin; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; GOSK: Gynaecologic Oncology Society of Kenya, G-CSF: Granulocyte colony stimulating factor; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria, TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Table 6. Summary of GOSK recommendations for the management of ultra high-risk GTN

Domain	GOSK recommendations
Criteria	• Manage patients with Ultra-High-Risk GTN through a multidisciplinary team. • Consider Ultra-High-Risk GTN in patients with any of the following: 1. FIGO score >12 2. Patients with liver and brain metastases
Chemotherapy	• Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). • Administer low-dose induction with Etoposide and Cisplatin followed by multi-agent chemotherapy. • Low-dose induction chemotherapy is administered weekly for one to three weeks as follows: Etoposide 100 mg/m2 IV infusion (day 1 and 2), Cisplatin 20 mg/m2 IV infusion (day1 and 2). • Recommended multi-agent chemotherapy regimen includes the following: EMA-CO, EMA-EP, EP-EMA (see dosages in Tables 2 and 3 above). • Administer G-CSF support to avoid treatment delays due to myelosuppression (see dosages in Tables 2 and 3 above).
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. • Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. Review complete blood count, liver function tests, and renal function tests.
Contraception	Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria.
Consolidation	• Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). • Administer four cycles of consolidation chemotherapy.
BEP: Bleomycin, Etoposide, Cisplatin; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; GOSK: Gynaecologic Oncology Society of Kenya, G-CSF: Granulocyte colony stimulating factor; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria, TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Table 7. Summary of GOSK recommendations for the management of placental site trophoblastic tumor (PSST) and epithelioid trophoblastic tumor (ETT)

Domain	GOSK recommendations
Approach and treatment modality	• Manage Placental Site Trophoblastic Tumor (PSST) and Epithelioid Trophoblastic Tumor (ETT) through a multidisciplinary team (MDT). • Hysterectomy is the primary treatment modality because PSTT and ETT are relatively chemo-resistant compared with other forms of GTN. • HCG may not be useful in treatment monitoring unless initially raised. • Patients should be on appropriate contraception guided by the WHO MEC on contraceptives. Stage I • Antecedent pregnancy <48 months: Perform hysterectomy followed by surveillance. • Antecedent pregnancy ≥48 months: Perform hysterectomy followed by platinum-based chemotherapy (EMA-EP, EP-EMA, TP/TE, BEP, VIP, or ICE). (see dosages in Table 2 and 3 above) Stages II-IV • Hysterectomy is performed followed by adjuvant chemotherapy such as EP-EMA (Etoposide, cisplatin, methotrexate, and actinomycin D). • TP/TE is administered where the antecedent pregnancy is more than 48 months.
BEP: Bleomycin, Etoposide, Cisplatin; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D, GOSK: Gynaecologic Oncology Society of Kenya, GTN: Gestational Trophoblastic Neoplasia; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria, TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Table 8. Summary of GOSK recommendations for special considerations, post-treatment surveillance, and supportive and palliative care

Domain	GOSK recommendations
Special Considerations	*Hemorrhage:* In vaginal bleeding, consider vaginal packing using adrenaline-soaked gauze. Manage uterine hemorrhage with internal iliac artery ligation or hysterectomy. *CNS metastases:* Treatment modalities include low-dose induction chemotherapy followed by multi-agent chemotherapy, neurosurgery for intracranial hemorrhage, and radiotherapy. *Role of surgery*: Surgical intervention may be considered in selected patients with GTN following MDT discussion, such as hysterectomy for persistent uterine-confined chemo-resistant disease and for placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT).
Post-treatment surveillance	*Low-risk GTN:* Perform monthly clinical assessment and monitoring of hCG for one year. Offer combined oral contraceptives for the period of surveillance (see Tables 2-6 for details). *High-risk GTN and ultra-high-risk GTN:* Perform monthly clinical assessment and monitoring of hCG for two years. Offer contraceptives for the period of surveillance (see Tables 2-6 for details). *Placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor*: • Perform monthly clinical assessment for six months, then 3-monthly for year 2, then 6-monthly for years 4 and 5, then annually for the next 5 years. • Offer contraceptives for 2 years. Afterwards, the childbearing decision is individualized.
Supportive and Palliative Care	• Ensure comprehensive documentation of clinical findings, investigations, treatment, and follow-up plans. • Perform routine clinical assessment for treatment-related complications, comorbidities, and chronic health conditions • Provide counselling regarding fertility preservation, contraception during surveillance, future reproductive planning, and pregnancy outcomes following treatment.
GOSK: Gynaecologic Oncology Society of Kenya; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin.	

Table 9. Summary of GOSK recommendations for the management of recurrent GTN

Domain	GOSK recommendations
Criteria	• Patient with recurrent GTN must be discussed in a multidisciplinary team (MDT) • Recurrent GTN should be treated as high-risk GTN. • Criteria for recurrent GTN include the following: 1. Rising hCG levels following normalization and completion of treatment, including consolidation therapy. 2. New evidence of disease recurrence after remission.
Chemotherapy	• Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). • Regimens: EMACO, EMA-EP (see dosages in Tables 2 and 3 above). • Recommended treatment should be individualized according to prior treatment exposure, recurrence pattern, and risk stratification. • Consider salvage multi-agent chemotherapy, including the following: EMA-EP, EP-EMA, TP/TE, ICE, or other platinum-based regimens.
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. • Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. Review complete blood count, liver function tests, and renal function tests.
Contraception	Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria.
Consolidation	• Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). • Administer three cycles of consolidation chemotherapy for high-risk GTN and four cycles for ultra-high risk GTN.
BEP: Bleomycin, Etoposide, Cisplatin; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; GOSK: Gynaecologic Oncology Society of Kenya; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

1.0 Introduction

1.1 Background

Gestational trophoblastic neoplasia (GTN) refers to a group of malignant disorders arising from the abnormal proliferation of trophoblastic tissue following a hydatidiform mole or a non-molar pregnancy (1). Gestational trophoblastic disease (GTD) describes a spectrum of conditions derived from placental trophoblastic tissue, including hydatidiform moles and the malignant forms collectively classified as GTN. GTN comprises four principal histological types: invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Choriocarcinoma is generally the most aggressive histological type (1). These conditions differ in their histological characteristics, biological behavior, and clinical management.

GTN is highly sensitive to chemotherapy. The overall survival of patients with low-risk GTN approaches 100%, while that of patients with high-risk GTN approaches 90%. These favorable outcomes are attributable to improved diagnosis and treatment, including quantitative human chorionic gonadotropin (hCG) monitoring and structured post-molar follow-up. These advances have contributed particularly to improved outcomes in countries with specialized GTN treatment centers (1,6–11). The high overall cure rates are important because most patients with GTN are of childbearing age and may wish to preserve their fertility.

1.2 Epidemiology

The global incidence of GTN varies significantly across geographical regions, potentially reflecting genetic, environmental, and health care-related factors. Reported incidence is higher in Southeast Asia, Latin America, and Africa than in North America and Europe (1). The incidence of choriocarcinoma has been reported at approximately 23 per 100,000 deliveries in Southeast Asia, compared with 3 per 100,000 deliveries in Europe and North America (1). PSTT and ETT are rare entities, with reported incidences of approximately 1 per 100,000 deliveries and 0.1 per 100,000 deliveries, respectively (1).

Approximately 50% of GTN cases arise following a molar pregnancy, 25% following pregnancy loss or ectopic pregnancy, and 25% following a term or preterm pregnancy (4). When GTN develops following a molar pregnancy, it may present as an invasive mole or choriocarcinoma and, less commonly, as PSTT or ETT. Approximately 15% of patients with a complete hydatidiform mole develop local invasion, while 5% develop metastatic disease. GTN, usually non-metastatic, occurs in approximately 1%–4% of patients following a partial hydatidiform mole (5).

There are limited data on the burden of GTN in Africa because of the scarcity or absence of comprehensive cancer registries in many countries. An average incidence of 0.38 cases per 100,000 women of reproductive age has been reported. However, the actual incidence is thought to be higher, potentially approaching that reported in Southeast Asia (1,2). The burden of GTN in Africa is compounded by late presentation and limited access to diagnostic and treatment resources, which may contribute to increased morbidity and mortality. These challenges have also been highlighted in a ten-year study of GTN conducted at a Kenyan hospital (3). Lower socioeconomic status and poor maternal nutrition have also been suggested as possible contributing factors, although their associations with GTN risk require further clarification (2).

1.3 GTN in Kenya

Data on the burden of GTN in Kenya remain limited. The ten-year study conducted at a Kenyan hospital highlights the challenges associated with the diagnosis and management of GTN in the country (3). As in other sub-Saharan African settings, limitations in cancer registration and access to diagnostic and treatment resources may constrain accurate estimation of the national disease burden and contribute to delays in diagnosis and treatment. The management of GTN in Kenya has historically been heterogeneous across institutions, potentially contributing to disparities in the care delivered to affected patients. These challenges highlight the need for coordinated diagnostic evaluation, appropriate risk stratification, timely access to effective treatment, and structured post-treatment surveillance.

1.4 Rationale for the GOSK protocol

GTN is a highly curable malignancy when diagnosed promptly and managed appropriately. However, optimal outcomes depend on accurate diagnosis, appropriate risk stratification, timely initiation of treatment, access to effective chemotherapy, and structured post-treatment surveillance. These requirements may be challenging in settings where specialized services and treatment resources are limited.

In Kenya, the absence of standardized national clinical management protocols has contributed to heterogeneous treatment approaches and potential inequities in care. Recognizing this gap, the Gynaecologic Oncology Society of Kenya (GOSK) initiated the development of standardized national clinical management protocols for GTN. These protocols have been developed through the adaptation of high-quality international guidelines to the Kenyan health care context. The overarching objectives of the GOSK protocol are to harmonize clinical practice, enhance diagnostic accuracy, optimize treatment outcomes, promote the efficient use of available resources, and reduce disparities in the quality of care delivered to patients with GTN across the country. The protocol provides recommendations on diagnostic evaluation, risk-stratified management of low-risk, high-risk, and ultra-high-risk GTN, management of PSTT and ETT, special clinical considerations, post-treatment surveillance, supportive and palliative care, and recurrent disease.

2.0 Risk factors, Clinical presentation, Histology and staging

2.1 Risk factors for gestational trophoblastic neoplasia

Several factors have been associated with an increased risk of developing gestational trophoblastic neoplasia (GTN), particularly following a molar pregnancy. Maternal age is an important consideration, with the risk of GTN reported to range from 30% to 60% among patients older than 40 years. A history of recurrent molar pregnancy is also associated with an approximately threefold increase in the risk of developing GTN.

Features associated with a high tumor burden include uterine enlargement greater than 4 weeks above that expected for gestational age, a serum human chorionic gonadotropin (hCG) level of at least 100,000 mIU/mL, and bilateral theca-lutein cysts measuring at least 6 cm. The presence of any of these features has been associated with an increased risk of invasive mole, reported in the source as approximately 40%–50%.

Geographic and ethnic variations in the incidence of GTN have also been reported, with higher rates observed in Southeast Asia. Genetic factors may contribute to susceptibility to recurrent gestational trophoblastic disease, with mutations in NLRP7 and KHDC3L associated with recurrent molar pregnancies. Some reports have also suggested an association between blood groups A and AB and a higher incidence of GTN. In addition, delayed evacuation of a molar pregnancy has been associated with an increased risk of subsequent GTN.

2.2 Clinical features for gestational trophoblastic neoplasia

The clinical presentation of gestational trophoblastic neoplasia (GTN) varies according to the antecedent pregnancy, extent of disease, and histologic subtype, as summarized in Table 10.

Table 10. Clinical features of gestational trophoblastic neoplasia

Clinical feature	Description
Abnormal vaginal bleeding	• This is the most common symptom • Heavy, persistent, or irregular bleeding after a molar pregnancy, miscarriage, or childbirth. • May be associated with the passage of grape-like vesicular tissue.
Uterine enlargement disproportionate to gestational age	This is due to excessive trophoblastic proliferation.
Pelvic pain or pressure	This is due to an enlarged uterus or theca-lutein cysts.
Metastatic symptoms	• Lungs: dyspnea, hemoptysis, cough, chest pain • Brain: headache, seizures, neurologic deficits • Liver: jaundice, right upper quadrant pain, hepatomegaly. • Vagina: bluish or purple nodules, vaginal bleeding
Persistently elevated hCG levels	Abnormal proliferation of trophoblastic tissue
hCG: human chorionic gonadotropin	

2.3 Histologic types of gestational trophoblastic neoplasia

GTN comprises four main histologic types: choriocarcinoma, invasive mole, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Their distinguishing characteristics are summarized in Table 11.

Table 11. Histologic types of gestational trophoblastic neoplasia and their characteristics

Characteristic	Histologic type			
	Choriocarcinoma	**Invasive mole**	**PSTT**	**ETT**
Histology	Syncytiotrophoblasts and cytotrophoblasts without villous structures	Hydropic villi with trophoblastic proliferation invading the myometrium	Mononuclear intermediate trophoblasts infiltrating the myometrium	Resembles squamous cell carcinoma histologically
Origin	Any type of pregnancy: molar, normal, ectopic	Hydatidiform mole, most commonly a complete mole	Intermediate trophoblast of the implantation site	Chorionic-type intermediate trophoblast
Genetic composition	Androgenetic (from mole) or biparental (from normal pregnancy)	Androgenetic (paternal DNA only)	Biparental -maternal and paternal	Biparental -maternal and paternal
Ploidy	Variable (diploid/aneuploid)	Diploid (46, XX/46, XY)	Diploid (46, XX/46, XY)	Diploid (46, XX/46, XY)
Malignant potential	Highly malignant, rapidly invades blood vessels, metastasizes early to lungs, vagina, liver, and brain	Locally invasive, rarely metastasizes	Slow growing, but can be locally aggressive	May present as a well-circumscribed uterine or extrauterine mass

Characteristic	Histologic type			
	Choriocarcinoma	**Invasive mole**	**PSTT**	**ETT**
HCG levels	High	High	Low	Low
Frequency of GTN	20-30%	50-60%	1-2%	<1%
Response to chemotherapy	Extremely responsive	Responsive	Less responsive, surgery is often done	Least responsive, often requires surgery
ETT: epithelioid trophoblastic tumor; hCG: human chorionic gonadotropin; PSST: placental site trophoblastic tumor.				

2.4 Diagnosis of gestational trophoblastic disease

The diagnosis of post-molar gestational trophoblastic neoplasia (GTN) is based primarily on serial serum human chorionic gonadotropin (hCG) measurements and histologic findings, according to the FIGO criteria summarized in Table 12.

Table 12. FIGO criteria for diagnosis of post-molar gestational trophoblastic neoplasia

Criterion	Definition
Plateauing hCG levels	Less than 10% change in four consecutive hCG measurements over a period of at least 3 weeks (days 1, 7, 14, and 21).
Rising hCG levels	Greater than 10% increase in three consecutive weekly hCG measurements over a period of at least 2 weeks (days 1, 7, and 14).
Histologic diagnosis	Histologic confirmation of choriocarcinoma.

FIGO: International Federation of Gynecology and Obstetrics; hCG: human chorionic gonadotropin.

2.5 Staging and risk assessment

The staging and risk assessment of GTN combine the FIGO anatomical staging system (Table 13) and the WHO prognostic scoring system, modified as the FIGO score (Table 14). The prognostic score incorporates eight factors associated with the risk of resistance to single-agent chemotherapy.

Table 13. FIGO staging of gestational trophoblastic neoplasia

Stage	Description
I	Disease confined to the uterine corpus
II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina)
III	GTN extends to the lungs, with or without genital tract involvement
IV	All other metastatic sites

Table 14. WHO prognostic scoring system modified as the FIGO score

Risk factor	Score			
	0	1	2	4
Age (years)	<40	≥40	_	_
Antecedent pregnancy	Mole	Abortion	Term	_
Interval months from the end of the index pregnancy to treatment	<4	4 – 6	7 -12	>12
Pretreatment serum hCG (mIU/ml)	$<10^3$	$>10^3$ - 10^4	$>10^4$ - 10^5	$>10^5$
Largest tumor size, including uterus (cm)	_	3-4	≥ 5	_
Site of metastases	Lung	Spleen, kidney	GIT	Brain, liver
Number of metastases	_	1-4	5-8	>8
Previous failed chemotherapy	_	_	Single drug	≥2 drugs

- To ensure accurate scoring, it is critical to use the beta-hCG level at the time of treatment for GTN and not the beta-hCG level at the time of diagnosis or evacuation of a molar pregnancy source.
- Low-risk GTN: WHO score 0-6
- High-risk: WHO GTN 7-12
- Ultra-high-risk GTN: WHO score >12. This category is associated with features such as a a non-molar antecedent pregnancy, brain metastases, and failed prior multi-agent chemotherapy.

The modified WHO prognostic scoring system is not applicable to placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT). Risk assessment and treatment selection for these subtypes should instead be guided by disease stage, histologic subtype, and other relevant prognostic features.

FIGO: International Federation of Gynecology and Obstetrics; GIT: gastrointestinal tract; hCG: human chorionic gonadotropin

3.0 Protocol Objectives

3.1 Broad objective

To establish a standardized, evidence-based approach to the management of gestational trophoblastic neoplasia (GTN) in Kenya.

3.2 Specific objectives

This protocol provides recommendations and guidance on:

1. Diagnostic evaluation of GTN.
2. Management of low-risk GTN.
3. Management of high-risk GTN.
4. Management of ultra-high-risk GTN.
5. Management of placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT).
6. Special clinical considerations, including hemorrhage, central nervous system metastases, and the role of surgery.
7. Post-treatment surveillance.
8. Supportive and palliative care.
9. Management of recurrent GTN.

4.0 Clinician responsibility

This protocol represents the evidence-based consensus of the multidisciplinary development group under the Gynaecologic Oncology Society of Kenya (GOSK) for the management of patients with gestational trophoblastic neoplasia (GTN). It is intended to guide clinical practice; however, the application of its recommendations should always be informed by independent clinical judgment and consideration of each patient's individual circumstances.

5.0 Methods

5.1 Protocol development approach

This protocol was developed using an adaptation approach, drawing on existing high-quality international guidelines and tailoring their recommendations to Kenya's health system and resource context. The process aimed to align the protocol with internationally accepted standards while addressing the specific challenges of the Kenyan healthcare setting.

5.2 Development panel

A multidisciplinary protocol development panel was convened, comprising gynecologic oncologists, pathologists, radiologists, gynecologic oncology nurses, oncology pharmacists, radiation oncologists, public health specialists, and patient representatives. The panel received technical orientation from experts at the University of Nairobi and Kenyatta National Hospital on the principles of evidence-based guideline adaptation. The training emphasized the use of standardized appraisal tools, systematic methods for evaluating published guidelines and protocols, and approaches for contextualizing recommendations to local realities.

5.3 Search strategy

A comprehensive search was conducted in PubMed and Google Scholar to identify relevant evidence-based guidelines, systematic reviews, and best-practice statements on the management of gestational trophoblastic neoplasia (GTN). The search terms included "Gestational Trophoblastic Neoplasia," "clinical guideline," "gynecologic oncology," "protocols," and "guidelines." Six primary reference guidelines were identified and are summarized in **Table 15**.

Table 15. Summary of retrieved guidelines

Title	Type	Publisher	Year of last update
National Cancer Comprehensive Network (NCCN) Clinical Practice Guidelines in Oncology: Gestational Trophoblastic Neoplasia[13]	Clinical Guideline	NCCN	2025
Diagnosis And Management of Gestational Trophoblastic Disease: FIGO 2021 Update[9]	Clinical Guideline	FIGO	2021
Management Of Gestational Trophoblastic Disease. Green-Top Guideline No. 38[14]	Clinical Guideline	Royal College of Obstetricians and Gynecologists (RCOG)	2020
Practical clinical guidelines of the European Organization for the Treatment of Trophoblastic Disease (EOTTD) for treatment and referral of gestational trophoblastic disease (2020)[15]	Clinical Guideline	(EOTTD) For Treatment and Referral of Gestational Trophoblastic Disease	2020
Guideline No. 408: Management Of Gestational Trophoblastic Diseases[16]	Clinical Guideline	Society of Obstetricians and Gynecologists of Canada (SOGC)	2021
Management Of Gestational Trophoblastic Disease (2020)[17]	Clinical Guideline	Royal Australian and New Zealand College of Obstetrician/Gynecologists (RANZOG)	2020

5.4 Appraisal and selection of guidelines

All retrieved guidelines were independently appraised by two trained panelists using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, which evaluates guideline quality across six domains:

1. Scope and purpose;

2. Stakeholder involvement;
3. Rigor of development;
4. Clarity of presentation;
5. Applicability; and
6. Editorial independence.

Where the two reviewers did not reach consensus, one of the facilitators acted as a tiebreaker to reach a final decision.

Each domain was scored using a 7-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Domain scores were converted into percentages using the following formula:

Standardized domain score (%) = (Obtained score – Minimum possible score) ÷ (Maximum possible score – Minimum possible score) × 100.

Although all six domains were assessed, particular emphasis was placed on rigor of development (Domain 3) and clarity of presentation (Domain 4) to ensure methodological robustness. Guidelines scoring below 80% in Domain 3 or below 90% in Domain 4 were excluded from further consideration.

Based on these criteria, four guidelines: the National Comprehensive Cancer Network (NCCN), International Federation of Gynecology and Obstetrics (FIGO), European Organisation for the Treatment of Trophoblastic Disease (EOTTD), and Society of Obstetricians and Gynaecologists of Canada (SOGC) were selected for inclusion in the analysis of recommendations. Their appraisal scores and selection decisions are presented in Table 16.

Table 16. Source guideline appraisal and scores

Title	Domain 1 %	Domain 2 %	Domain 3 %	Domain 4 %	Domain 5 %	Domain 6 %	Overall Decision
National Comprehensive Cancer Network (Guidelines)-version 2 2025 Gestational Trophoblastic Neoplasia	100	75	91	100	44	100	Included
Diagnosis and management of gestational trophoblastic disease: FIGO 2021 update	100	72	83	100	36	79	Included
Management of Gestational Trophoblastic Disease. Green-top Guideline No. 38 (2020)	100	100	74	85	40	88	Excluded
Practical clinical guidelines of the EOTTD for treatment and referral of gestational trophoblastic disease (2020)	100	78	84	97	46	83	Included
Society of Obstetricians and Gynecologists of Canada (SOGC) Guideline No. 408: Management of Gestational Trophoblastic Diseases (2021)	100	86	85	100	31	79	Included
Management of gestational trophoblastic disease (2020). The Royal Australian and New Zealand College of Obstetrician/Gynecologists (RANZOG)	100	89	73	82	40	88	Excluded

6.0 Review of evidence

6.1 Diagnostic evaluation for gestational trophoblastic neoplasia

The diagnostic evaluation for GTN consists of clinical assessment, laboratory investigations, imaging, and in some cases histology, as outlined in Table 17.

Table 17. Comparative evidence from source guidelines for diagnostic evaluation for gestational trophoblastic neoplasia

Diagnostic evaluation	NCCN	FIGO	SOGC	EOTTD
History	Obtain the history of Vaginal bleeding and pregnancy outcomes	Obtain the history of vaginal bleeding, pregnancy outcomes, and features of metastases	Obtain the history of vaginal bleeding, dyspnea, cough	Obtain the history as part of the molar-diagnostic pathway, vaginal bleeding
Physical examination	Perform a general, systemic, and pelvic examination and a speculum examination	Perform a general, systemic, and pelvic examination and a speculum examination	Perform a general and systemic examination	Perform a general, systemic, and pelvic examination and a speculum examination
Laboratory	Evaluate CBC, LFT, RFTs, and TFTs	Evaluate CBC, LFTs, and RFTs	Evaluate CBC, LFTs, RFTs, and CSF	Evaluate CBC, LFTs, and RFTs
HCG	Serial assays for diagnosis	Serial assays	Serial assays	Serial assays
Imaging	A pelvic ultrasound is used to confirm the absence of pregnancy. Perform a	Pelvis ultrasound, Chest x-ray; if metastases are	Pelvis ultrasound	Pelvis ultrasound (Doppler)

Diagnostic evaluation	NCCN	FIGO	SOGC	EOTTD
	chest X-ray; if metastases are present, perform chest/abdomen/pelvis CT scan with contrast, brain MRI with or without contrast	present, chest/abdomen/pelvis CT scan with contrast, and brain MRI with or without contrast	CT scan chest and abdomen, MRI brain, no advantage of FGD PET scan over other imaging	Chest x-ray; if metastases are present, do chest/abdomen/pelvis CT scan with contrast, and brain MRI with or without contrast
Pathology histology	Not required for confirmation of diagnosis Histologic type: invasive choriocarcinoma PSTT, ETT	Not required for confirmation of diagnosis	Not required for confirmation of diagnosis	Not required for confirmation of diagnosis
IHC	Mel-CAM, p63, hPL, Ki-67	No mention	No mention	No mention

CBC: complete blood count; CSF: cerebrospinal fluid; CT scan: computed tomography scan; EOTTD: European Organization for the Treatment of Trophoblastic Disease; ETT: epithelioid trophoblastic tumor; FGD PET scan: Fluorodeoxyglucose positron emission tomography; FIGO: International Federation of Gynecology and Obstetrics; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; hPL: human placental lactogen; IHC: Immunohistochemistry; LFTS: liver function tests; Mel-CAM: melanoma cell adhesion molecule; MRI: magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; PSST: placental site trophoblastic tumor; RFTs: renal function tests; SOGC: Society of Obstetricians and Gynecologists of Canada

6.2 Management of low-risk GTN

6.2.1 Triage of patients in the management of low-risk GTN

The management of low-risk GTN begins with patient triage based on the WHO score, hCG levels, and histology (Table 18). The appropriate chemotherapy and monitoring are then instituted (Table 19). The criteria and approach to the management of second-line GTN are outlined in Table 20.

Table 18. Comparative evidence from source guidelines for triaging of patients in the management of low-risk GTN

WHO Score	NCCN	FIGO	SOGC	EOTTD
0-4	Single agent-methotrexate or actinomycin D	Single agent-methotrexate or actinomycin D	Single agent methotrexate or actinomycin D	Single-agent Methotrexate (mostly used) or Actinomycin D
5-6	Single agent methotrexate or actinomycin D	• Score of 5-6 without choriocarcinoma: single agent methotrexate or actinomycin D • Score of 5–6 with diagnosis of choriocarcinoma: consider multiple-agent chemotherapy	• Single-agent methotrexate or actinomycin D • Patients at risk of resistant disease	Single-agent Methotrexate (mostly used) or Actinomycin D
HCG	No mention	No mention	• Single agent methotrexate or actinomycin D • Patients at risk of resistant disease: pre-treatment hCG levels in excess of 400 000 mIU/mL	No mention
Non-molar choriocarcinoma	No mention	No mention	•Single agent methotrexate or actinomycin D • Patients at risk of resistant disease	No mention

EOTTD: European Organization for the Treatment of Trophoblastic Disease; FIGO: International Federation of Gynecology and Obstetrics; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; mIU: milli International Unit; mL: milliliter; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada; WHO: World Health Organization

Table 19. Comparative evidence from source guidelines for first-line management of low-risk GTN

Management	NCCN	FIGO	SOGC	EOTTD
Chemotherapy	• **Methotrexate (Preferred)**	• **Methotrexate** 1. Methotrexate-Folinic Acid	• **Methotrexate** 1. 1 mg/kg IM every 48 hours x4,	• **Methotrexate (preferred)**

Management	NCCN	FIGO	SOGC	EOTTD
	1. 0.4 mg/kg/day (max 25 mg/day) IV push (preferred) or IM daily x 5 days; repeat every 14 days 2. 1 mg/kg IM every other day x 4 days (Days 1, 3, 5, and 7). Alternating every other day with leucovorin 0.1 mg/kg or 15 mg PO (preferred); repeat every 14 days • **Actinomycin D** 1. Preferred dosing option: 0.5 mg fixed dose IV push daily x 5 days, repeat every 14 days 2. 1.25 mg/m^2 (max 2 mg) IV push pulse; repeat every 14 days	8-day regimen (50 mg) IM days 1, 3, 5, 7 with folinic acid 15 mg orally on days 2, 4, 6, 8); repeat every 2 weeks. 2. Methotrexate 0.4 mg/kg (max. 25 mg) IV or IM for 5 days every 2 weeks. • **Actinomycin D** 1. Actinomycin D pulse 1.25 mg/m2 IV every 2 weeks. 2. Actinomycin D 0.5 mg IV for 5 days every 2 weeks.	folinic acid 30 mg PO every 48 hoursx4 (30 hours after methotrexate) every 2 weeks 2. 0.4 mg/kg (max 25 mg) IV or IM daily for 5 days every 2 weeks • **Actinomycin D** 1. Actinomycin D pulse 1.25 mg/m^2 IV every 2 weeks. 2. Actinomycin D 9−13 ug/kg (maximum 0.5 mg) IV for 5 days every 2 weeks.	• **Actinomycin D** As an alternative to Methotrexate given after consultation with the GTD center
Treatment monitoring	HCG every 2 weeks, at the start of each treatment cycle	HCG every 2 weeks	HCG-same lab	HCG at least every two weeks
Contraception	Oral contraceptives	Contraception	Contraception	Contraception
Consolidation	2 cycles	2−3 cycles	2-3 cycles	
Hysterectomy	Recommended for localized disease in the uterus when fertility preservation is not desired	Not highly recommended-patient will still need chemotherapy, hCG monitoring	Recommended if completed childbearing	Recommended if completed childbearing
EOTTD: European Organization for the Treatment of Trophoblastic Disease; FIGO: International Federation of Gynecology and Obstetrics; GTD: Gestational Trophoblastic Disease; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; IM: Intramuscular; IV: Intravenous; mg: Kg: kilogram; milligram; mIU: milli-international unit; mL: milliliter; NCCN: National Comprehensive Cancer Network; PO: Per oral; SOGC: Society of Obstetricians and Gynecologists of Canada, ug: microgram.				

Table 20. Comparative evidence from source guidelines for second-line management of low-risk GTN

Management	NCCN	FIGO	SOGC	EOTTD
Definition and approach	Poor response to initial therapy: • hCG level plateaus (<10% change) for 3 treatment cycles or • hCG level rises (>10% change) for 2 treatment cycles	• HCG level plateaus • hCG rises during treatment • Toxicity precludes an adequate dose or frequency of treatment.	• A plateau of or a rise in hCG levels. • Restaging and risk scoring to switch to an alternate single-agent (revised risk score ≤6) or multi-agent treatment.	• Primary resistance: after the initial two courses, if hCG is rising, change treatment. If hCG plateaus (<10% change), continue to the third course and if still plateaued, change treatment. • Acquired resistance after initial response: hCG plateau (<10%) over two courses (4 wks) or rise over at least 2 wks
Chemotherapy	• Good response to initial therapy followed by hCG level plateau or re-elevation (initial treatment hCG<1000 IU/L): • Change to single agent not used in first-line therapy e.g. Methotrexate to Actinomycin D • Actinomycin D 0.5 mg fixed dose IV push daily for 5 days, repeat every 14 days • Consider hysterectomy with salpingectomy • **Poor response (**if	• Alternate single agent • Consider multiple agents-EMA-CO • Salvage therapies: EMA-EP, EP-EMA, BEP, Immunotherapy with pembrolizumab (avelumab not recommended)	Alternate single-agent (revised risk score ≤6) or multi-agent treatment.	Methotrexate resistance: • Re-imaging • change treatment as advised by the GTD Centre • Options: 1. If hCG <1000 IU/L use Actinomycin D 2. If hCG > 1000 IU/L use EMA-CO • hysterectomy if attained desired family size.

Management	NCCN	FIGO	SOGC	EOTTD
	hCG level plateaus for 2 treatment cycles or beta-hCG level rises (>10% change) for 1 treatment cycle): Repeat workup to check for metastasis, WHO rescoring, and transition to combination therapy: EMA-CO • Good response to initial therapy followed by hCG level plateau or re-elevation (initial treatment beta-hCG >1000 IU/L) or Poor response to initial therapy: Change from a single-agent systemic therapy to combination EMA-CO and repeat workup to check for metastasis, Recalculate the WHO score based on imaging and Consider hysterectomy • Poor response (if hCG level plateaus for 2 treatment cycles or hCG level rises (>10% change) for 1 treatment cycle): Administer platinum-based regimens (TP/TE, BEP, VIP, ICE, TIP), immunotherapy, and surgical resection if feasible			
Treatment monitoring	HCG every 2 weeks, at the start of each treatment cycle	No mention	No mention	No mention
Contraception	Offer contraception	Offer contraception	Offer contraception	Offer contraception
Consolidation	Administer 3 cycles	Administer 3 cycles	Administer 3 cycles	Administer 3 cycles

BEP: Bleomycin, Etoposide, Cisplatin; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EOTTD: European Organization for the Treatment of Trophoblastic Disease; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; FIGO: International Federation of Gynecology and Obstetrics; GTD: Gestational Trophoblastic Disease; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; IU/L: International Unit/Liter; IV: Intravenous; mIU: milli-International Unit; mL: milliliter; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.

6.3 Management of high-risk GTN

The first-line and second-line management of high-risk GTN are outlined in Tables 21 and 22.

Table 21. Comparative evidence from source guidelines for first-line management of high-risk GTN

Management	NCCN	FIGO	SOGC	EOTTD
Definition and approach	High-risk GTN confirmed: ≥7 Prognostic score Or Stage IV	Risk score of 5–6 with diagnosis of choriocarcinoma: Consider multiple-agent chemotherapy	FIGO score 7-12	• Suspected high-risk GTN (FIGO score 7-12), extensive imaging (CT chest and abdomen, and if necessary, MRI pelvis and brain, all with contrast). • Management in the GTD center

Management	NCCN	FIGO	SOGC	EOTTD
Chemotherapy regimen	EMA-CO	EMA-CO	EMA-CO or EMA-EP	EMA-CO
Treatment monitoring	HCG assay every 2 weeks during treatment	hCG every 2 weeks during treatment	hCG weekly	hCG assay every 2 weeks during treatment
Contraception	Offer oral contraceptives	Offer contraception	Offer contraception	Offer contraception
Consolidation	Administer 3–4 cycles once normal hCG levels are achieved	Administer 3–4 cycles	Administer 3 cycles	Administer 2–4 cycles or as advised by the GTD center

CT scan: computed tomography scan; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EOTTD: European Organization for the Treatment of Trophoblastic Disease; FIGO: International Federation of Gynecology and Obstetrics; GTD: Gestational Trophoblastic Disease; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; MRI: magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada

Table 22. Comparative evidence from source guidelines for second-line management of high-risk GTN

Management	NCCN	FIGO	SOGC	EOTTD
Definition and approach	≥7 Prognostic score or Stage IV with good response on EMA-CO followed by hCG plateau at low levels or incomplete response to treatment	Patients who do not attain a complete response with EMA-CO	• Resistant disease is diagnosed if there is a plateau of or a rise in hCG levels • Management in specialized centers	• Primary resistance: after initial two courses, if hCG is rising, change treatment. If hCG plateaus (<10% change), continue to the third course, and if still plateaued, change treatment. Acquired resistance after initial response: hCG plateau (<10%) over two courses (4 wks) or rise over at least 2 wks • Management in GTD center
Chemotherapy	• EMA-EP or EP-EMA • Alternative therapy for patients who are intolerant to EP-EMA: Platinum-based regimens with bleomycin, Ifosfamide, or paclitaxel, immunotherapy-pembrolizumab • G-CSF as primary prophylaxis • Resection for chemotherapy-resistant disease if feasible	Salvage therapies: • EP-EMA • TP/TE • VIP • ICE • BEP • Immunotherapy -pembrolizumab	➢ Chemotherapy Options: • EMA-EP • TP/TE • ICE • BEP • Immunotherapy-pembrolizumab • HER2 antagonists: trastuzumab, lapatinib ➢ Surgical resection of isolated foci ➢ High-dose chemotherapy with autologous bone marrow or stem cells transplantation	
Treatment monitoring	HCG before treatment cycle	No mention	No mention	No mention
Contraception	Offer contraception	Offer contraception	Offer contraception	Offer contraception
Consolidation	No mention	No mention	No mention	No mention

BEP: Bleomycin, Etoposide, Cisplatin; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EOTTD: European Organization for the Treatment of Trophoblastic Disease; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; FIGO: International Federation of Gynecology and Obstetrics; G-CSF-Granulocyte-Colony Stimulating Factor; GTD: Gestational Trophoblastic Disease; GTN: Gestational Trophoblastic Neoplasia; HERS 2: human epidermal growth factor receptor 2/neu receptor antagonists; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin.

6.3 Management of ultra-high-risk GTN

The approach to and management of ultra-high-risk GTN are outlined in **Table 23.** Patients with ultra-high-risk GTN need low-dose induction chemotherapy before the multi-agent chemotherapy.

Table 23. Comparative evidence from source guidelines for management of ultra-high-risk GTN

Management	NCCN	FIGO	SOGC	EOTTD
Definition and approach	metastatic disease with FIGO score >12	FIGO score >12 and liver, brain, or extensive metastases	FIGO score >12 or patients with liver and brain metastases	• FIGO score >12 • Referral to the GTD center is mandatory
Chemotherapy regimen	• Low-dose induction: Etoposide and Cisplatin followed by EMA-CO • G-CSF support • If poor response to EMA-CO, then EMA-EP or EP-EMA	• Low-dose induction: Etoposide and Cisplatin followed by EP-EMA or TE/TP, EMA-CO with dose adjustments in brain metastases • Options in case of resistance to EP-EMA or TE/TP: MBE, VIP, ICE, BEP, immunotherapy-pembrolizumab	Low -dose induction-Etoposide and Cisplatin followed by EMA-EP (preferred especially with liver metastases), EMA-CO	• Low -dose induction-Etoposide and Cisplatin followed by EP-EMA, EMA-EP (preferred in liver and brain metastases), EMA-CO • G-CSF support
Treatment monitoring	HCG before treatment cycle	hCG before treatment cycle	hCG before treatment cycle	hCG before treatment cycle
Contraception	Offer contraception	Offer contraception	Offer contraception	Offer contraception
Consolidation	Administer 4 cycles	Administer 4 cycles	Administer 4 cycles	Administer 4 cycles

BEP: Bleomycin, Etoposide, Cisplatin; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EOTTD: European Organization for the Treatment of Trophoblastic Disease; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; FIGO: International Federation of Gynecology and Obstetrics; G-CSF-Granulocyte-Colony Stimulating Factor; GTD: Gestational Trophoblastic Disease; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin.

6.4 Management of placental site trophoblastic tumor and epitheliod trophoblastic tumor

Placental site trophoblastic tumor and epithelioid trophoblastic tumor are managed according to the stage and the period before the antecedent pregnancy (Table 24).

Table 24. Comparative evidence from source guidelines for management of placental site trophoblastic tumor and epithelioid trophoblastic tumor

Guideline	Recommendations
NCCN	• Non-metastatic (stage I): Hysterectomy with salpingectomy ± pelvic lymph node biopsy • Metastatic: Hysterectomy with salpingectomy, excision of metastatic disease if feasible, and chemotherapy with a platinum-based regimen-EMA-EP, EP-EMA, or other regimens-TP/TE, BEP, VIP, or ICE
FIGO	• Hysterectomy -primary mode of treatment in most cases. • For fertility preservation, especially in a localized lesion, conservative management is considered: uterine curettage, hysteroscopic resection, and chemotherapy. • In advanced stage-EP-EMA or TE/TP. • Interval from antecedent pregnancy of more than 48 months and/or Stage IV disease, additional experimental therapies (pembrolizumab)
EOTTD	**Stage I** • Antecedent pregnancy < 48 months: ➢ Hysterectomy + surveillance • Antecedent pregnancy ≥ 48 months: ➢ Hysterectomy + platinum-based combination chemotherapy (EP-EMA) + surveillance. ➢ High dose chemotherapy ➢ Experimental treatment (pembrolizumab). **Stage II-III** • Antecedent pregnancy < 48 months: ➢ Hysterectomy + platinum-based combination chemotherapy -EP-EMA + resection of any visible residual disease post chemotherapy + surveillance. ➢ Radical hysterectomy is done depending on the location of the lesion. Suspicious lymph nodes removed for staging or debulking purposes. • Antecedent pregnancy ≥ 48 months:

Guideline	Recommendations
	➢ Hysterectomy + platinum-based combination chemotherapy (e.g. EP-EMA) + resection of any visible residual disease post chemotherapy + surveillance. ➢ High-dose chemotherapy or experimental treatment is considered (pembrolizumab). **Stage IV** • Antecedent pregnancy < or ≥ 48 months: ➢ Hysterectomy + platinum-based combination chemotherapy (EP-EMA) + resection of visible residual disease post chemotherapy + surveillance. ➢ Other options: high-dose chemotherapy or other experimental treatment (pembrolizumab).
SOGC	**Stage I** • Simple hysterectomy with ovarian preservation • Eight weeks of adjuvant EMA-EP or paclitaxel-cisplatin/paclitaxel etoposide TP/TE in risk factors- antecedent pregnancy more than 48 months before diagnosis **Stage II to IV** • Combination of chemotherapy with EMA-EP or TP/TE and surgery • Consolidation chemotherapy for 8 weeks
BEP: Bleomycin, Etoposide, Cisplatin; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EOTTD: European Organization for the Treatment of Trophoblastic Disease; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; FIGO: International Federation of Gynecology and Obstetrics; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin.	

3. Special considerations (hemorrhage in GTN, CNS metastases, role of surgery)

Special considerations in the management of GTN include hemorrhage, CNS metastases, and the role of surgery (Table 25).

Table 25. Comparative evidence from source guidelines for special considerations (hemorrhage, CNS metastases, and role of surgery)

	NCCN	FIGO	SOGC	EOTTD
Hemorrhage	• Uterine artery embolization • Hysterectomy	• Uterine artery embolization • Hysterectomy • Laparotomy-control bleeding in the GIT, liver, kidney, spleen	• Uterine artery embolization • Hysterectomy	• Embolization • Hysterectomy
CNS metastases	**Chemotherapy-** Induction chemotherapy, then intensive chemotherapy, intrathecal methotrexate, and increased methotrexate dosage **Surgery-** Raised ICP, active intracranial hemorrhage, impending cerebral herniation **Radiotherapy-** Stereotactic body radiation therapy (SBRT), whole brain radiation.	**Chemotherapy**-Induction chemotherapy, then intensive chemotherapy (EP-EMA), intrathecal methotrexate, increased methotrexate in EMA-CO, longer consolidation-4 cycles. **Neurosurgery** 1. Raised ICP 2. Intracranial hemorrhage **Radiotherapy-**brain metastases	**Chemotherapy**- low-dose induction chemotherapy, intensive chemotherapy (EP-EMA), longer consolidation, 4 cycles. **Neurosurgery** 1. Raised ICP 2. Intracranial hemorrhage **Radiotherapy-** Stereotactic body radiation therapy (SBRT)	**Chemotherapy-**Induction chemotherapy, intensive chemotherapy (EP-EMA), intrathecal methotrexate, increased methotrexate in EMA-CO, longer consolidation-4 cycles. **Surgery** **Radiotherapy**
Role of surgery	**Hysterectomy** 1. Low-risk disease- to reduce the number of cycles 2. Uterine-confined chemo-resistant disease 3. Hemorrhage-control bleeding 4. In PSST/ETT- Hysterectomy with salpingectomy ± pelvic lymph	**Hysterectomy** 1. To control bleeding through laparoscopy or an open approach. 2. In Low-risk disease, to reduce the number of treatment cycles 2. In uterine-confined chemo-resistant lesions 3. In PSTT and ETT 4. **Lung resection-**For metastases-chemo-resistant lesions	**Hysterectomy** 1. Uterine-confined chemo-resistant 2. hemorrhage-control bleeding 3. In PSTT and ETT	**Hysterectomy** 1. Uterine-confined chemo-resistant 2. In PSTT and ETT

	NCCN	FIGO	SOGC	EOTTD
	node biopsy **Lung metastases: resection** of chemo-resistant lesions **Craniotomy** 1. Raised ICP, 2. Active intracranial hemorrhage 3. Impending cerebral herniation	**Neurosurgery** 1. Raised ICP 2. Intracranial hemorrhage		
EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EOTTD: European Organization for the Treatment of Trophoblastic Disease; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; ETT: epithelioid trophoblastic tumor; FIGO: International Federation of Gynecology and Obstetrics; GIT: gastrointestinal tract; hCG: human chorionic gonadotropin; ICP: Intracranial pressure; NCCN: National Comprehensive Cancer Network; PSST: placental site trophoblastic tumor; SBRT: Stereotactic body radiation Therapy; SOGC: Society of Obstetricians and Gynecologists of Canada.				

6.5 Post-treatment surveillance

The treatment of GTN is followed by post-treatment surveillance to detect any recurrence, which includes clinical assessment, beta-hCG monitoring, contraception, and imaging (Tables 26-28).

Table 26. Comparative evidence from source guidelines for post-treatment surveillance for low-risk GTN

	NCCN	FIGO	SOGC	EOTTD
HCG monitoring	Monthly for one year	Monthly for at least a year	Weekly 4-6 weeks, then monthly for a year	Weekly for a month, then monthly for a year. HCG and placenta evaluated in subsequent pregnancies
Contraception	Combined contraceptives preferred	Reliable contraception for one year.	Reliable contraception for one year.	Contraception for one year.
Imaging	Not routinely done	No recommendation	Baseline imaging	Re-imaging previous abnormal areas as baseline
EOTTD: European Organization for the Treatment of Trophoblastic Disease; ETT: epithelioid trophoblastic tumor; FIGO: International Federation of Gynecology and Obstetrics; hCG: human chorionic gonadotropin; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada.				

Post-treatment surveillance for high-risk GTN and ultra-high-risk GTN

Table 27. Comparative evidence from source guidelines for post-treatment surveillance for high-risk GTN and ultra-high-risk GTN

Parameter	NCCN	FIGO	SOGC	EOTTD
HCG monitoring	Monthly for at least one year	Monthly for at least one year	Weekly 4-6 weeks, then monthly for a year, then monthly for 2 years	Weekly 4-6 weeks, then monthly for a year, then monthly for one year, reducing frequency for 5 years
Contraception	Combined oral contraceptives	Reliable contraception for one year	Reliable contraception for two years -	Reliable contraception. Older women for one year.
Imaging	If brain metastases, MRI 6-12 monthly for 2-3 yrs	No mention	baseline imaging	Whole body baseline imaging after treatment
EOTTD: European Organization for the Treatment of Trophoblastic Disease; ETT: epithelioid trophoblastic tumor; FIGO: International Federation of Gynecology and Obstetrics; hCG: human chorionic gonadotropin; MRI: magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada.				

Post-treatment surveillance for placental site trophoblastic tumor and epithelioid trophoblastic tumor

Table 28. Comparative evidence from source guidelines for post-treatment surveillance for placental site trophoblastic tumor and epithelioid trophoblastic tumor

	NCCN	FIGO	SOGC	EOTTD
HCG monitoring	Monthly-duration	No recommendation	No mention	If slightly elevated -imaging for follow-up

	NCCN	FIGO	SOGC	EOTTD
				If elevated, weekly for 6 weeks, then monthly for 12 months, then reducing rates for 10 years.
Contraception	No recommendation	No recommendation	Duration of follow-up	No recommendation
Imaging	Follow-up after treatment; hCG is a less reliable tumor marker. FGD PET scan (whole body) after chemotherapy and then FGD PET scan or CT chest abdominal-pelvic every 6–12 months for 2–3	No recommendation	No recommendation	Done according to the GTD center

EOTTD: European Organization for the Treatment of Trophoblastic Disease; FGD-PET scan: Fluorodeoxyglucose positron emission tomography; FIGO: International Federation of Gynecology and Obstetrics; GTD: Gestational Trophoblastic Disease; hCG: human chorionic gonadotropin; MRI: magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada.

Supportive and palliative care

Supportive and palliative care in GTN involves a multidisciplinary team and encompasses general medical care, counselling and coordination with the patient, the family and other care providers (**Table 29**).

Table 29. Comparative evidence from source guidelines for supportive and palliative treatment

	NCCN	FIGO	SOGC	EOTTD
Supportive care and survivorship	1. Document history, physical examination, and provide test results- imaging, laboratory 2. Regular general medical care – side effects of medicine, chronic disease, genitourinary symptoms, and adoption of a healthy lifestyle. 3. Communication and coordination- clinicians involved in the care of survivors, primary care clinicians, and other specialists 4. Provide a summary of treatment and follow-up recommendations. 5. Subsequent pregnancy: early ultrasound to confirm intrauterine pregnancy, perform pathologic evaluation of placenta, evaluate hCG at 6 weeks postpartum to confirm return to negative 5.Survivor/family education and counselling, workplace policies	1. Counselling- future fertility, pregnancy, and offspring (not affected). 2. Psychosocial counselling throughout care	Referral for genetic counseling and testing should be arranged for women with recurrent gestational trophoblastic disease, as this is a rare scenario that may be associated with a familial gene mutation	Psychosocial counselling throughout care
Palliative care	Consider supportive care instead of chemotherapy in poor prognosis- PSTT, ETT	No mention		No mention

EOTTD: European Organization for the Treatment of Trophoblastic Disease; ETT: Epithelioid Trophoblastic Tumor; FIGO: International Federation of Gynecology and Obstetrics; hCG: human chorionic gonadotropin; MRI: magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; PSST: Post-Treatment surveillance for Placental Site Trophoblastic Tumor; SOGC: Society of Obstetricians and Gynecologists of Canada.

Management of recurrent GTN

The management of recurrent GTN, including the approach, criteria, treatment, and monitoring, is outlined in Table 30.

Table 30. Comparative evidence from source guidelines for management of recurrent GTN

Management	NCCN	FIGO	SOGC	EOTTD
Definition and approach	Relapse from Remission		• Restaging with a CT scan of the head, chest, abdomen, and pelvis.	• Rise of hCG after normalization and cessation of treatment, including consolidation • Two sequential rising hCG values (at least one week apart) above the reference level of the GTD center

Management	NCCN	FIGO	SOGC	EOTTD
			• FGD-PET scan to localize foci of resistant/recurrent disease and target therapy • Rescoring the low- or high-risk treatment options selected	
Chemotherapy regimen	1.EMA/EP Or EP/EMA 2. Consider alternative therapy for patients who are intolerant to EP/EMA: Platinum-based regimens with bleomycin, Ifosfamide, or paclitaxel **1.** Additional Agents/Regimens -Pembrolizumab, Avelumab		• Chemotherapy options (high-risk disease): EMA-EP, TP/TE, ICE, and BEP • Multi-drug-resistant disease: immunotherapy (pembrolizumab) or HERS 2 antagonists. • Surgical resection for isolated foci of persistent tumor. Beta-hCG is used to assess the acute response to surgical intervention. • High-dose chemotherapy with autologous bone marrow or stem cell transplantation	
Treatment monitoring	No mention	No mention	No mention	No mention
Contraception	No mention	No mention	No mention	No mention
Consolidation	No mention	No mention	No mention	No mention

BEP: Bleomycin, Etoposide, Cisplatin; CT scan: computed tomography scan; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EOTTD: European Organization for the Treatment of Trophoblastic Disease; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; FGD-PET scan: Fluorodeoxyglucose positron emission tomography; FIGO: International Federation of Gynecology and Obstetrics; GTN: Gestational Trophoblastic Neoplasia; HERS 2: human epidermal growth factor receptor 2/neu receptor antagonists; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; NCCN: National Comprehensive Cancer Network; SOGC: Society of Obstetricians and Gynecologists of Canada; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin.

7.0 GOSK recommendations

Diagnostic evaluation for GTN

The diagnostic evaluation for GTN consists of clinical assessment, laboratory investigations, imaging, and in some cases, histology as outlined in Table 31.

Table 31. GOSK recommendations for diagnostic evaluation of gestational trophoblastic neoplasia

Domain	GOSK Recommendations
History	Obtain a comprehensive history including age, abnormal vaginal bleeding, cough, dyspnea, type of antecedent pregnancy (molar, miscarriage, term pregnancy, interval months from the end of the index pregnancy to treatment, and, if recently treated for GTN, whether there is previous failed chemotherapy.
Physical examination	Perform a comprehensive physical examination to include the following: 1. General examination to elicit possible anemia due to bleeding, and respiratory distress due to lung metastasis.

Domain	GOSK Recommendations
	2. Pelvic examination with bimanual examination to evaluate uterine enlargement and presence of bilateral adnexal masses due to theca-lutein cysts. Pelvic assessment is done with caution to avoid triggering massive hemorrhage in cases of vaginal metastases. 3. Speculum examination to assess for vulvar and vaginal metastases.
HCG monitoring	Perform quantitative serum hCG testing for all patients with suspected GTN. In patients with prior molar pregnancy, serial hCG monitoring should be used during post-treatment surveillance-weekly monitoring for three weeks until normalization (≤ 5 mIU/ml), then monthly for six months. Plateauing or rising hCG levels suggest development of GTN (FIGO Criteria for Diagnosis of Post-Molar Gestational Trophoblastic Neoplasia)[1]
Laboratory investigations	Consider performing a routine pregnancy test in all women, irrespective of age, as part of a general evaluation. A positive pregnancy test is followed by quantitative hCG levels. Perform complete blood count (CBC), liver function tests (LFTs), and renal function tests (RFTs) as baseline tests and to evaluate for possible metastases. Thyroid function tests (TFTs) should be performed in patients with hCG levels >100,000 mIU/mL to evaluate for hyperthyroidism.
Imaging	An abdominal and pelvic ultrasound is done to rule out a pregnancy and to check the adnexa and any liver metastases. A chest X-ray is performed initially; if metastases are suspected or identified, perform a contrast-enhanced CT scan of the chest, abdomen, and pelvis, and a contrast-enhanced brain MRI. Imaging is also used to evaluate for the largest tumor size, including the uterus (cm), site of metastases, and number of metastases. Non-contrast MRI may be considered when contrast administration is contraindicated or contrast-enhanced imaging is unavailable. Perform an FDG PET scan where resources allow.
Pathology (Histology)	Obtaining a biopsy should generally be avoided because of the risk of severe hemorrhage. Histologic confirmation is not required for diagnosis; however, where tissue is available, histology may assist in differentiating GTN subtypes.
Immunohistochemistry (IHC)	Conduct immunohistochemistry studies where biopsy tissue is available to support histologic characterization.

[1]FIGO Criteria for Diagnosis of Post-Molar Gestational Trophoblastic Neoplasia:
1. *Plateau of beta-hCG levels (<10% change): Four measurements over a period of 3 weeks or longer (days 1,7,14, and 21).*
2. *Rising beta-hCG levels (>10% change): Three consecutive weekly measurements over at least a period of 2 weeks or more (days 1,7, and 14).*
3. *Histologic diagnosis of choriocarcinoma.*

CBC: complete blood count; CT scan: computed tomography scan; FIGO: International Federation of Gynecology and Obstetrics; GOSK: Gynaecologic Oncology Society of Kenya; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; LFTS: liver function tests; MRI: magnetic resonance imaging; RFTS: renal function tests.

Guiding principles for the diagnosis and management of GTN

The guiding principles for the diagnosis and management of GTN are as follows:

1. FIGO Criteria for Diagnosis of Post-Molar Gestational Trophoblastic Neoplasia.
2. Staging and Risk Assessment. This includes the FIGO Staging of Gestational Trophoblastic Neoplasia (Table 13) and the WHO scoring system, based on prognostic factors and modified as the FIGO score (Table 14).
3. Non-molar antecedent pregnancy, such as a term pregnancy, has different prognostic implications. GTN with an antecedent term pregnancy is invariably a choriocarcinoma, which is treated with multi-agent chemotherapy.
4. HCG greater than 100,000 mIU/ml - high levels of hCG are due to a high tumor burden, and therefore consideration for multi-agent chemotherapy must be made.

Management of low-risk GTN

The management of low-risk GTN begins with patient triage based on the WHO score, hCG levels, and histology (**Table 32**). The appropriate chemotherapy and monitoring are then instituted (**Table 33**). Patients with low-risk GTN are treated with single-agent chemotherapy with Methotrexate or actinomycin D; however, low-risk GTN patients with a significant risk of developing chemoresistance should be triaged for initial multi-agent treatment with EMA-CO as outlined in **Table 34**. The criteria and approach to the management of second-line GTN are outlined in **Table 35**.

Risk stratification

Table 32. GOSK recommendations on risk stratification and initial treatment selection for low-risk GTN

Parameter	GOSK recommendations
WHO Score 0-4	Treat with single-agent chemotherapy using methotrexate or actinomycin D.
WHO Score 5-6	• Patients with a WHO score of 5–6 without choriocarcinoma should receive single-agent chemotherapy (methotrexate or actinomycin D). • Patients with GTN following a non-molar pregnancy should be treated as high risk irrespective of the score. • Patients with a WHO score of 5–6 with choriocarcinoma should be managed with multi-agent chemotherapy (EM-ACO).

Parameter	GOSK recommendations
Pre-treatment hCG	Patients with a WHO score of 5–6 and pre-treatment hCG ≥100,000 mIU/mL should be considered as high risk for resistant disease and should be managed with multi-agent chemotherapy (EM-ACO).
EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, hCG: human chorionic gonadotropin	

Table 33. GOSK recommendations on first-line management of low-risk GTN

Management	GOSK recommendations
Definition and Approach	• There are two categories of low-risk GTN patients: category one, patients who require single-agent chemotherapy, and category two, patients who require multi-agent chemotherapy. • Category One • In low-risk GTN, where the WHO score is 0-4, serum hCG is < 100,000 mIU/ml, there is no histological diagnosis of choriocarcinoma, and there is no evidence of metastases, the recommended first-line treatment is single-agent chemotherapy with methotrexate or actinomycin D. • Category Two • In low-Risk GTN, where the WHO score is 5 or 6, serum hCG is >100,000 mIU/ml, or there is a confirmed histological diagnosis of choriocarcinoma, massive per vaginal bleeding, and metastases are present, the recommended first-line treatment is multi-agent chemotherapy (EMACO). Manage all patients with GTN through a multidisciplinary team
Chemotherapy	• Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). • Category One (Patients who require single agent chemotherapy) 1. Methotrexate 1 mg/kg IM on Days 1, 3, 5, and 7, alternating with folinic acid 15 mg orally on Days 2, 4, 6, and 8, every 2 weeks. OR 2. Methotrexate 0.4 mg/kg/day IV for 5 days, every 2 weeks. OR 3. Actinomycin D 0.5 mg IV for 5 days, every 2 weeks. OR • 4. Actinomycin D pulse 1.25mg/m^2 IV, every 2 weeks (when hCG <3000 mIU/ml). • Category Two (Patients who require multi-agent chemotherapy) EMA-CO regimen (every two weeks) Etoposide 100mg/m^2 IV infusion (days 1 and 2) Actinomycin D 0.5mg IV bolus (days 1 and 2) Methotrexate 300 mg/m^2 IV infusion (day 1), Leucovorin 15 mg IM or PO q12 hours x 4 (days 2 and 3), Cyclophosphamide 600 mg/m^2 IV infusion (day 8) Vincristine (oncovin) 1 mg/m^2 IV bolus (day 8).
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	▪ Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. ▪ Assess for possible organ toxicity through clinical assessment and investigations such as complete blood count, liver function tests, renal function tests, and address side effects/toxicity as appropriate.
Contraception	• Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria[17]. • Counsel patients regarding the avoidance of pregnancy during treatment and post-treatment surveillance.
Consolidation	▪ Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). ▪ For single-agent chemotherapy, administer two more cycles of consolidation chemotherapy. ▪ For multi-agent chemotherapy (EMA-CO), administer three more cycles of consolidation chemotherapy.
EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; GOSK: Gynaecologic Oncology Society of Kenya, GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; MEC: Medical Eligibility Criteria; WHO: World Health Organization.	

Table 34. GOSK recommendations on second-Line management of low-risk GTN

Management	GOSK recommendations
Definition and approach	• Manage all patients with GTN through a multidisciplinary team. • Patients with poor response to initial therapy, defined as: 1. hCG plateau (<10% change) over 3 treatment cycles. 2. hCG rise (>10% change) over 2 treatment cycles. 3. Refractory organ toxicity due to initial single-agent chemotherapy
Pre-requisites before initiation of second-line treatment	1. Perform clinical assessment, including history and physical examination. 2. Perform baseline investigations including complete blood count, liver function tests, and renal function tests. 3. Repeat metastatic workup including CT scan chest, CT scan abdomen–pelvis, and brain MRI if brain metastases are suspected and an FDG PET scan where resources allow. 4. Perform the Modified WHO Prognostic Scoring System as adapted by FIGO.

Management	GOSK recommendations
Chemotherapy	• Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). • EMACO is the preferred second-line regimen administered as indicated above in Table 33. • In poor response to EMA-CO, the recommended second-line chemotherapy regimen includes: EMA-EP or EP-EMA and platinum-based regimens (TP/TE, BEP, VIP, ICE). EMA-EP regimen (every two weeks): Etoposide 100 mg/m^2 IV infusion over 1 hour (day 1) Methotrexate 300 mg/m^2 IV infusion over 12 hours (day 1) Actinomycin D 0.5 mg IV bolus (day 1) Leucovorin 15 mg IM or PO q12 hours x 4 (days 2 and 3) Etoposide 100-150 mg/m^2 IV infusion over 1 hour (day 8) Cisplatin 75 mg/m^2 IV infusion over 2 hours (day 8) Granulocyte colony-stimulating factor support:5 mcg/kg SC (days 9-14) EMA-EP regimen (every two weeks): Etoposide 100–150 mg/m^2 IV over 1 hour (day 1) Cisplatin 75 mg/m^2 IV over 2 hours (day 1) Etoposide 100 mg/m2 IV over 1 hour (day 8) Methotrexate 300 mg/m^2 IV infusion over 12 hours (day 1) Leucovorin 15 mg PO (preferred) or IM every 12 hours for 4 doses beginning 24 hours after the start of the methotrexate infusion Actinomycin D 0.5 mg IV push (day 1) Granulocyte colony-stimulating factor support:5 mcg/kg SC (days 3-6 and 10-13).
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	▪ Perform clinical assessment including history and physical examination to look out for drug side effects. These are addressed as appropriate, including counselling and drug adjustments. Evaluate hCG levels at the start of each treatment cycle. ▪ Assess for possible organ toxicity through clinical assessment and investigations such as complete blood count, liver function tests, renal function tests, and address side effects/toxicity as appropriate.
Contraception	• Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria. • Counsel patients regarding the avoidance of pregnancy during treatment and post-treatment surveillance.
Consolidation	▪ Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). ▪ Treatment discontinuation should occur only after three consecutive normalizations of hCG values are achieved across three treatment cycles.
BEP: Bleomycin, Etoposide, Cisplatin; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D, FGD PET scan-Fluorodeoxyglucose positron emission tomography, CT scan-computed tomography scan; GOSK: Gynaecologic Oncology Society of Kenya, GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria; MRI: magnetic resonance imaging; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Management of high-risk GTN

The first-line and second-line management of high-risk GTN is outlined in Tables 35 and 36.

Table 35. GOSK recommendations on first-line management of high-risk GTN

Management	GOSK recommendations
Definition and approach	• Involve a multidisciplinary team (MDT) in the management of High-Risk GTN • Recommended criteria for first-line management for High-Risk GTN: 1. FIGO score 7-12 2. Stage IV disease
Chemotherapy	• Chemotherapy is administered until normalization of hCG result (≤5 mIU/mL). • Administer EMA-CO as the preferred first-line chemotherapy regimen (see Table 32 above for dosages).
Treatment monitoring	• Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. • Assess for possible organ toxicity through clinical assessment and investigations such as complete blood count, liver function tests, renal function tests, and address side effects/toxicity as appropriate.
Premedication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. • Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.

Management	GOSK recommendations
Contraception	• Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria. • Counsel patients regarding the avoidance of pregnancy during treatment and post-treatment surveillance.
Consolidation	• Continue chemotherapy until normalization of hCG (≤5 mIU/mL), followed by three more cycles of consolidation chemotherapy. • Treatment discontinuation should occur only after three consecutive normalizations of hCG values are achieved across three treatment cycles.
EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; GOSK: Gynaecologic Oncology Society of Kenya; GTN: Gestational Trophoblastic Neoplasia, hCG: human chorionic gonadotropin; MEC: Medical Eligibility Criteria; WHO: World Health Organization.	

Table 36. GOSK recommendations for second-line management of high-risk GTN

Management	GOSK recommendations
Definition and approach	• Involve a multidisciplinary team (MDT) in the management of High-Risk GTN • Recommended criteria for second-line treatment for High-Risk GTN: 1. Incomplete response to EMA-CO, defined as a plateau or rise in hCG levels. 2. Stage IV disease with initial response to EMA-CO followed by hCG plateau or incomplete response to treatment.
Prerequisites before initiation of second-line treatment:	1. Perform clinical assessment, including history and physical examination. 2. Perform baseline investigations including complete blood count (CBC), liver function tests (LFTS), and renal function tests (RFTS). 3. Repeat metastatic workup including CT scan chest, CT scan abdomen–pelvis, and brain MRI if brain metastases are suspected and an FDG PET scan where resources allow.
Treatment modality	Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). Recommended second-line treatment modalities include: 1. EMA-EP or EP-EMA. 2. EMA-EP plus bevacizumab. 3. Alternative regimens for patients who are intolerant to EMA-EP: • Platinum-based regimens (TP/TE†, VIP, ICE, BEP) • Immunotherapy (pembrolizumab) 4. Administer G-CSF as primary prophylaxis of myelosuppression where indicated. 5. Consider resection of chemotherapy-resistant disease where feasible following MDT discussion.
Premedication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. • Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	▪ Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. ▪ Assess for possible organ toxicity through clinical assessment and investigations such as complete blood count, liver function tests, renal function tests, and address side effects/toxicity as appropriate.
Contraception	• Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria. • Counsel patients regarding the avoidance of pregnancy during treatment and post-treatment surveillance.
Consolidation	• Continue chemotherapy until normalization of hCG (≤5 mIU/mL), followed by three more cycles of consolidation chemotherapy. • Treatment discontinuation should occur only after three consecutive normalizations of hCG values are achieved across three treatment cycles.
BEP: Bleomycin, Etoposide, Cisplatin; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; GOSK: Gynaecologic Oncology Society of Kenya, G-CSF: Granulocyte colony stimulating factor; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria, TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Management of ultra-high-risk GTN

The approach to and management of ultra-high risk GTN are outlined in Table 37. Patients with ultra-high-risk GTN need low-dose induction chemotherapy before the multi-agent chemotherapy.

Table 37. GOSK recommendations on management of ultra-high-risk GTN

Management	GOSK recommendations
Definition and approach	• Manage patients with Ultra-High-Risk GTN through a multidisciplinary team (MDT). • Consider Ultra-High-Risk GTN in patients with any of the following: 1. FIGO score >12 2. Patients with liver and brain metastases
Chemotherapy	• Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). • Administer low-dose induction with Etoposide and Cisplatin followed by multi-agent chemotherapy. • Low-dose induction chemotherapy is administered weekly for one to three weeks as follows: Etoposide 100 mg/m^2 IV infusion (day 1 and 2), Cisplatin 20 mg/m^2 IV infusion (day1 and 2). • Recommended multi-agent chemotherapy regimen includes the following: EMA-CO, EMA-EP, EP-EMA (see dosages in Tables 33 and 34 above). • Administer G-CSF support to avoid treatment delays due to myelosuppression (see dosages in Tables 33 and 34 above).
Pre-medication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. • Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	▪ Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. ▪ Assess for possible organ toxicity through clinical assessment and investigations such as complete blood count, liver function tests, renal function tests, and address side effects/toxicity as appropriate.
Contraception	• Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria. • Counsel patients regarding the avoidance of pregnancy during treatment and post-treatment surveillance.
Consolidation	▪ Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). ▪ Continue chemotherapy until normalization of hCG (≤5 mIU/mL), followed by four more cycles of consolidation chemotherapy. ▪ Treatment discontinuation should occur only after four consecutive normalizations of hCG values are achieved according to treatment response and surveillance protocol.
BEP: Bleomycin, Etoposide, Cisplatin; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D; GOSK: Gynaecologic Oncology Society of Kenya, G-CSF: Granulocyte colony stimulating factor; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria, TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Management of placental site trophoblastic tumor and epithelioid trophoblastic tumor

Placental site trophoblastic tumor (PSST) and epithelioid trophoblastic tumor (ETT) are managed according to the stage and the period before the antecedent pregnancy (Table 38).

Table 38. GOSK recommendations on management of placental site trophoblastic tumor and epithelioid trophoblastic tumor

Management	GOSK recommendations
Guiding principles	• Manage PSTT and ETT through a multidisciplinary team (MDT). • Hysterectomy remains the primary treatment modality because PSTT and ETT are relatively chemo-resistant compared with other forms of GTN. • HCG may not be useful in treatment monitoring unless initially raised. • Patients should be on appropriate contraception guided by the WHO MEC on contraceptives.
Stage I	Antecedent pregnancy <48 months: • Perform hysterectomy followed by surveillance.
	Antecedent pregnancy ≥48 months: • Perform hysterectomy followed by platinum-based chemotherapy (EMA-EP, EP-EMA, TP/TE, BEP, VIP, or ICE). • Consider high-dose chemotherapy in selected patients with poor response or advanced disease. • Consider immunotherapy (e.g., pembrolizumab) in selected patients.
Stage II–III	Antecedent pregnancy <48 months: • Perform a hysterectomy followed by platinum-based chemotherapy. •. Resect visible residual disease post-chemotherapy where feasible. • Perform lymph node assessment/resection where clinically indicated.
	Antecedent pregnancy ≥48 months: • Perform a hysterectomy followed by platinum-based chemotherapy and resection of residual disease where feasible.

Management	GOSK recommendations
	• Consider administration of high-dose chemotherapy. •. Consider administration of immunotherapy (e.g., pembrolizumab).
Stage IV	▪ Perform a hysterectomy where feasible, followed by platinum-based chemotherapy. ▪ Consider resection of residual disease, high-dose chemotherapy, and immunotherapy according to disease burden, treatment response, and MDT recommendation.
BEP: Bleomycin, Etoposide, Cisplatin; EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D, GOSK: Gynaecologic Oncology Society of Kenya, GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Special considerations in GTN (hemorrhage, CNS metastases, role of surgery)

Special considerations in the management of GTN include hemorrhage, central nervous system (CNS) metastases, and the role of surgery (Table 39).

Table 39. GOSK recommendations on special considerations in GTN (hemorrhage, CNS metastases, role of surgery)

Domain	GOSK recommendations
Hemorrhage	Management of hemorrhage should be individualized according to bleeding source and hemodynamic status. 1. Vaginal bleeding: ▪ Consider vaginal packing using adrenaline-soaked gauze. 2. Uterine hemorrhage: ▪ Consider internal iliac artery ligation. ▪ Consider uterine artery embolization. ▪ Consider emergency hemostatic radiotherapy. ▪ Consider hysterectomy following Multidisciplinary team (MDT) discussion in patients with life-threatening hemorrhage, persistent uterine-confined chemo-resistant disease, or selected localized disease where reduction in chemotherapy burden is clinically justified. Hysterectomy remains the primary treatment modality for PSTT and ETT. 3. Gastrointestinal bleeding: ▪ Perform surgical intervention/arterial embolization where it is indicated to control bleeding from gastrointestinal metastases.
CNS metastases	Manage patients with CNS metastases through a multidisciplinary team (MDT). Chemotherapy: ▪ Administer low-dose induction chemotherapy with etoposide and cisplatin followed by multi-agent chemotherapy (e.g., EMA-CO). ▪ Low-dose induction chemotherapy is administered in 1 to 3 weeks (Etoposide 100 mg/m^2 IV infusion day 1 and day 2, Cisplatin 20 mg/m^2 IV infusion day 1 and day 2). ▪ Consider intrathecal methotrexate where it is possible to do a comprehensive CNS assessment including fundoscopy to rule out raised intracranial pressure. ▪ Consider IV high-dose methotrexate in selected patients where intrathecal methotrexate is contraindicated, or fundoscopy has not been done. ▪ Administer four courses of consolidation chemotherapy following hCG normalization according to treatment response. Surgery: ▪ Perform craniotomy for raised intracranial pressure, intracranial hemorrhage, or impending brain herniation. Radiotherapy: ▪ Consider stereotactic body radiation therapy (SBRT) for localized lesions that are chemo-resistant or the patient is not fit for surgery or not surgically accessible. ▪ Consider palliative whole-brain radiotherapy for symptomatic multifocal disease.
Role of surgery	Surgical intervention may be considered in selected patients with GTN following MDT discussion: **1.** Hysterectomy: ▪ Consider hysterectomy following multidisciplinary discussion in patients with persistent uterine-confined chemo-resistant disease, life-threatening uterine hemorrhage, or selected localized disease where reduction in chemotherapy burden is clinically justified. ▪ Hysterectomy remains the primary treatment modality for placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). **2.** Pulmonary surgery: ▪ Consider lung resection for chemo-resistant solitary pulmonary lesions. **3.** Neurosurgery: ▪ Perform neurosurgical intervention for raised intracranial pressure, intracranial hemorrhage, or impending brain herniation. 4. Any other site of localized disease that is chemo-resistant where surgical resection would give optimal outcomes.
EMACO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, vincristine; ETT: epithelioid trophoblastic tumor; GOSK: Gynaecologic Oncology Society of Kenya; GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICP: Intracranial pressure; PSST: placental site trophoblastic tumor; SBRT: Stereotactic body radiation therapy.	

Post-treatment surveillance

The treatment of GTN is followed by post-treatment surveillance to detect any recurrence, which includes clinical assessment, hCG monitoring, contraception, and imaging (Tables 40-42).

Table 40. GOSK recommendations on post-treatment surveillance for low-risk GTN

Follow-up parameter	GOSK recommendations	Frequency
Clinical assessment	• Obtain history for features of recurrence such as history of per vaginal bleeding and abdominal swelling. • Perform physical examination including systemic examination to look out for features of recurrence such as uterine enlargement. • Conduct wellness checks for cardiometabolic conditions • Discuss cancer screening-cervical, breast, and other cancers to be tailored to family history • Assess nutritional status	1 Year: Monthly for six months, then every three months for six months
Patient care coordination and linkages	• Refer and coordinate with other caregivers, such as physicians and counsellors, where necessary. • Offer advice to seek help for financial stability, insurance payments, and reintegration to work and daily activities.	Throughout surveillance
HCG monitoring	Monitor hCG using the same assay or laboratory where possible for quality assurance.	1 Year: Monthly for six months, then every three months for six months
Imaging	There is no role for routine imaging in the post-treatment surveillance of low-risk GTN unless there are indications such as an abdominal-pelvic ultrasound in per vaginal bleeding.	No imaging is done
Contraception	▪ Ensure effective contraception during surveillance; combined oral contraceptives should be offered as the preferred contraceptive choice where the patient fits the medical eligibility criteria for contraceptive use. ▪ Counsel on the avoidance of pregnancy during surveillance.	Throughout surveillance
Health promotion	Encourage a healthy lifestyle including balanced nutrition, regular physical activity, and smoking cessation.	Throughout surveillance
Psychosocial support	▪ Provide counselling on fertility, future reproductive planning, risk of recurrence, and long-term treatment effects. ▪ Assess psychological distress and provide support to patients, families, and caregivers. ▪ Address concerns regarding fertility, sexual health, body image, and fear of recurrence. ▪ Refer to fertility specialists, mental health services, or patient support groups where indicated.	Throughout surveillance

GOSK: Gynaecologic Oncology Society of Kenya; hCG: human chorionic gonadotropin.

Table 41. GOSK recommendations on post-treatment surveillance for high-risk and ultra-high-risk GTN

Follow-up parameter	GOSK recommendations	Frequency
Clinical assessment	▪ Assess for recurrence, metastases, and treatment-related adverse effects. ▪ Perform physical examination. ▪ Conduct wellness screening for cardiometabolic conditions. ▪ Discuss age- and risk-appropriate cancer screening (e.g., cervical, breast). ▪ Assess nutritional status.	Year 1: Monthly for six months, then every three months for six months Year 2: Every 3 months
Patient care coordination and linkages	• Coordinate multidisciplinary care (physicians, counsellors, social workers). • Provide support regarding finances, insurance, and reintegration into work and daily activities.	Throughout surveillance
HCG monitoring	Monitor hCG using the same assay or laboratory where possible for quality assurance.	Year 1: Monthly for six months, then every three months for six months Year 2: Every 3 months
Imaging	▪ Perform CT scan chest, CT scan abdomen–pelvis, and brain MRI according to disease burden and metastases. ▪ Perform an FDG PET scan where resources allow.	Year 1: Every 6 months Year 2: Every 6 months
Contraception	▪ Ensure effective contraception during surveillance; combined oral contraceptives should be offered as the preferred contraceptive choice where the patient fits the medical eligibility criteria for contraceptive use.	Throughout surveillance

Follow-up parameter	GOSK recommendations	Frequency
	▪ Counsel on the avoidance of pregnancy during surveillance.	
Health promotion	Encourage a healthy lifestyle including balanced nutrition, regular physical activity, and smoking cessation.	Throughout surveillance
Psychosocial support	▪ Provide counselling on fertility, future reproductive planning, risk of recurrence, and long-term treatment effects. ▪ Assess psychological distress and provide support to patients, families, and caregivers. ▪ Address concerns regarding fertility, sexual health, body image, and fear of recurrence. ▪ Refer to fertility specialists, mental health services, or patient support groups where indicated.	Throughout surveillance
CT scan-computed tomography scan; FGD PET scan- Fluorodeoxyglucose positron emission tomography; GOSK: Gynaecologic Oncology Society of Kenya; hCG-human chorionic gonadotropin; MRI: magnetic resonance imaging.		

Table 42. GOSK recommendations on post-treatment surveillance for placental site trophoblastic Tumor (PSTT) and epithelioid trophoblastic tumor (ETT)

Follow-up parameter	GOSK recommendations	Frequency
Clinical assessment	▪ Assess for recurrence, metastases, and treatment-related complications. ▪ Perform physical examination. ▪ Conduct wellness screening for cardiometabolic conditions and comorbidities. ▪ Discuss age- and risk-appropriate cancer screening (e.g., cervical, breast). ▪ Assess nutritional status.	Year 1: Monthly for six months, then every three months for six months Year 2: Every 3 months. Years 3–5: Every 6 months. Years 6–10: Annually
HCG monitoring	Monitor hCG according to baseline elevation and treatment response. Use the same assay/laboratory where possible.	Year 1: If initially elevated, monthly for six months, then every three months for six months Year 2: Every 3 months Years 3–5: Every 6 months Years 6–10: Discontinue if persistently normal and clinically stable
Imaging	▪ Perform CT scan chest, CT scan abdomen–pelvis, and brain MRI according to disease burden and metastases. ▪ Perform an FDG PET scan at completion of treatment where resources allow.	Year 1: CT scan chest/abdomen/pelvis every 6 months. Year 2: CT scan chest/abdomen/pelvis every 6 months. Years 3–5: CT scan chest/abdomen/pelvis every 6 months Years 6–10: Annual imaging where clinically indicated
Contraception and reproductive planning	Counsel regarding contraception, fertility, and future reproductive planning. Combined oral contraceptives may be used where appropriate or according to the WHO MEC on contraceptive use.	During active surveillance, individualize beyond Year 2
Health promotion	Encourage balanced nutrition, regular physical activity, smoking cessation, and management of chronic disease risk factors.	Throughout surveillance
Psychosocial support	▪ Provide counselling on fertility, future reproductive planning, recurrence risk, and long-term treatment effects. ▪ Assess psychological distress. ▪ Offer support to patients, families, and caregivers. ▪ Refer to fertility specialists, mental health services, or support groups where indicated.	Throughout surveillance
Patient care coordination and survivorship planning	Coordinate multidisciplinary follow-up and support reintegration into daily activities, work, finances, and long-term survivorship care.	Throughout surveillance
CT scan-computed tomography scan; FGD PET scan- Fluorodeoxyglucose positron emission tomography; GOSK: Gynaecologic Oncology Society of Kenya; hCG: human chorionic gonadotropin; MEC: Medical Eligibility Criteria; MRI: magnetic resonance imaging; WHO: World Health Organization.		

Supportive and palliative care

'An approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual[18]. Supportive and palliative

care in GTN involves a multidisciplinary team and encompasses general medical care, counselling and coordination with the patient, the family and other care providers (Table 43).

Table 43. GOSK recommendations on supportive care and palliative care

Domain	GOSK recommendations
Supportive care and survivorship	General supportive care and survivorship: • Ensure comprehensive documentation of clinical findings, investigations, treatment, and follow-up plans. • Provide patients with treatment summaries and individualized survivorship care plans. • Perform routine clinical assessment for treatment-related complications, comorbidities, and chronic health conditions. • Promote a healthy lifestyle including balanced nutrition, regular physical activity, and smoking cessation. • Provide patient and family education regarding disease course, treatment, surveillance, and long-term follow-up. • Facilitate multidisciplinary coordination among primary care providers, specialists, and supportive services. • Assess psychosocial well-being and provide counselling or referral where indicated.
Management of treatment-related effects	• Counsel patients that most chemotherapy-related adverse effects are transient and manageable. • Assess for acute and long-term toxicities, and institute appropriate supportive interventions. • Monitor for treatment-related complications and provide timely management according to toxicity profile.
Fertility and reproductive health	• Provide counselling regarding fertility preservation, contraception during surveillance, future reproductive planning, and pregnancy outcomes following treatment. • Counsel patients that future pregnancy is generally achievable following completion of treatment and recommended surveillance. • Recommend early obstetric assessment and first-trimester ultrasound in subsequent pregnancies. • Consider histopathological examination of the placenta following delivery in subsequent pregnancies. • Monitor hCG following subsequent pregnancy according to surveillance protocol.
Palliative care	• Consider early palliative care integration in patients with poor prognosis, refractory disease, significant symptom burden, or advanced PSTT/ETT. • Provide symptom control, psychosocial support, and goals-of-care discussions according to patient needs.
ETT: epithelioid trophoblastic tumor; GOSK: Gynaecologic Oncology Society of Kenya; hCG: human chorionic gonadotropin; PSST: placental site trophoblastic tumor.	

Management of recurrent GTN

The management of recurrent GTN, including the approach, criteria, treatment, and monitoring, is outlined in Table 44.

Table 44. GOSK rsecommendations on management of recurrent GTN

Management	GOSK recommendations
Definition and approach	• Patient with recurrent GTN must be discussed in a multidisciplinary team (MDT) at initiation of treatment and reviewed by MDT if progress is not good. • Recurrent GTN should be treated as high-risk GTN. • Criteria for recurrent GTN include the following: 1. Rising hCG levels following normalization and completion of treatment, including consolidation therapy. 2. New evidence of disease recurrence after remission. • Evaluation of recurrent GTN includes the following: 1. Restaging with contrast-enhanced imaging (CT chest, abdomen–pelvis, MRI, and brain imaging where indicated). 2. FDG-PET imaging, where localization of persistent or recurrent disease may influence management. 3. Repeat FIGO/WHO risk scoring. 4. Review of prior treatment exposure, chemotherapy resistance, and treatment-free interval. 5. Histologic reassessment where clinically indicated.
Chemotherapy	▪ Chemotherapy is administered until normalization of hCG (≤5 mIU/mL). ▪ Recommended chemotherapy for recurrent High Risk GTN (multi-agent chemotherapy) ○ EMA-CO ○ EMA-EP ▪ Recommended treatment should be individualized according to prior treatment exposure, recurrence pattern, and risk stratification. ▪ Consider salvage multi-agent chemotherapy, including the following: EMA-EP, EP-EMA, TP/TE, ICE, or other platinum-based regimens.

Management	GOSK recommendations
Role of surgery	▪ Consider surgical resection following multidisciplinary team (MDT) discussion in patients with localized chemo-resistant recurrent disease where complete excision is feasible. ▪ Consider hysterectomy in patients with persistent uterine-confined recurrent disease, life-threatening hemorrhage, or selected localized disease where a reduction in chemotherapy burden is clinically justified. ▪ Consider pulmonary resection for isolated chemo-resistant lung metastases. ▪ Consider neurosurgical intervention for recurrent CNS disease associated with raised intracranial pressure, intracranial hemorrhage, or impending brain herniation. ▪ Hysterectomy remains the primary treatment modality for placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT).
Premedication	• Pre-medication is administered before chemotherapy to prevent drug adverse effects such as nausea and vomiting, mucosal ulceration, and allergic reactions. Palonosetron 0.25mg IV stat, Dexamethasone 12 mg IV stat, Chlorpheniramine 10 mg IV stat, Esomeprazole 40 mg IV stat.
Treatment monitoring	▪ Perform clinical assessment and evaluate hCG levels at the start of each treatment cycle. ▪ Assess for possible organ toxicity through clinical assessment and investigations such as complete blood count, liver function tests, renal function tests, and address side effects/toxicity as appropriate.
Contraception	• Combined oral contraceptives, the most effective method, is offered as the preferred contraceptive choice for the duration of treatment and surveillance. Alternative contraceptive methods are offered in accordance with the WHO MEC criteria. • Counsel patients regarding the avoidance of pregnancy during treatment and post-treatment surveillance.
Consolidation	High-risk GTN: • Consolidation entails additional chemotherapy administered after normalization of hCG (≤5 mIU/mL). • Continue chemotherapy until normalization of hCG (≤5 mIU/mL), followed by three more cycles of consolidation chemotherapy. • The duration of consolidation therapy should be individualized based on treatment response, metastatic burden, and the multidisciplinary team (MDT) recommendation. Ultra-high-risk GTN: ▪ Continue chemotherapy until normalization of hCG (≤5 mIU/mL), followed by four more cycles of consolidation chemotherapy. ▪ The duration of consolidation therapy should be individualized based on treatment response, metastatic burden, and the multidisciplinary team (MDT) recommendation.
BEP: Bleomycin, Etoposide, Cisplatin; CNS: Central Nervous System: CT scan-computed tomography scan; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide; EMA-EP: Etoposide, Methotrexate, Actinomycin Etoposide, Cisplatin; EP-EMA: Etoposide, Cisplatin, Etoposide, Methotrexate, Actinomycin D, FGD PET scan-Fluorodeoxyglucose positron emission tomography, GOSK: Gynaecologic Oncology Society of Kenya, GTN: Gestational Trophoblastic Neoplasia; hCG: human chorionic gonadotropin; ICE: Ifosfamide, Carboplatin, Etoposide; MEC: Medical Eligibility Criteria; MRI: magnetic resonance imaging; TIP: Paclitaxel, Ifosfamide, Cisplatin; TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide; VIP: Etoposide, Ifosfamide, Cisplatin; WHO: World Health Organization.	

Chemotherapy regimen for GTN

Table 45. GOSK recommendations for single-agent chemotherapy regimen for low-risk GTN

Regimen	GOSK recommendations
Methotrexate	8-day regimen: Methotrexate 1 mg/kg and Folinic acid 1 mg/kg IM/IV on days 1, 3, 5, and 7; leucovorin 0.1 mg/kg rounded up to the nearest 5-mg dose increment or 15 mg PO (preferred) days 2,4,6, and 8; IV 50mg or IM 30 hours after each methotrexate dose on days 2, 4, 6, and 8. Repeat every 2 weeks
	8-day regimen: Methotrexate 50 mg and Folinic acid 50 mg IM on days 1, 3, 5, 7 with folinic acid 15 mg orally 24 h after methotrexate on days 2, 4, 6, 8. Repeat every 2 weeks.
	5-day regimen: Methotrexate 0.4 mg/kg/day, no Folinic acid 0.4 mg/kg/day (max 25 mg/day) IV push (preferred) or IM daily x 5 days. Repeat every 2 weeks
Actinomycin D	Pulse regimen:2 weeks 1.25 mg/m^2 (max 2 mg) IV push pulse. Repeat every 2 weeks
	5-day regimen 9−13 mg/kg (max 0.5 mg) IV for 5 days (DAYS1-5). Repeat every 2 weeks

Table 46. GOSK recommendations for multi-agent chemotherapy for GTN

Regimen	GOSK recommendations	
	Drug, dosage, route	**Administration**
EMA-CO	Etoposide 100mg/m^2 IV infusion	Days 1 and 2

Regimen	GOSK recommendations	
	Drug, dosage, route	**Administration**
(repeat every 2 weeks)	Methotrexate 300 mg/m2 IV infusion over 12 hours Actinomycin D 0.5mg IV bolus Leucovorin 15 mg IM or PO q12 hours x 4 Cyclophosphamide 600 mg/m^2 IV infusion Vincristine (oncovin) 1 mg/m^2 IV bolus	Day1 Days 1 and 2 Days 2 and 3 Day 8 Day 8
EMA-EP† **(repeat every 2 weeks, alternating EMA with EP)**	Etoposide 100 mg/m^2 IV infusion over 1 hour Methotrexate 300 mg/m^2 IV infusion over 12 hours Actinomycin D 0.5 mg IV bolus Leucovorin 15 mg IM or PO q12 hours x 4 Etoposide 100-150 mg/m^2 IV infusion over 1 hour Cisplatin 75 mg/m^2 IV infusion over 2 hours Granulocyte colony-stimulating factor support:5 mcg/kg SC	Day 1 Day 1 Day 1 Days 2 and 3 Day 8 Day 8 Days 9–14
EP-EMA† **(repeat every 2 weeks, alternating EP with EMA weekly)**	Etoposide 100–150 mg/m^2 IV over 1 hour Cisplatin 75 mg/m^2 IV over 2 hours Etoposide 100 mg/m2 IV over 1 hour Methotrexate 300 mg/m^2 IV infusion over 12 hours Leucovorin 15 mg PO (preferred) or IM every 12 hours for 4 doses beginning 24 hours after the start of the methotrexate infusion Actinomycin D 0.5 mg IV push Granulocyte colony-stimulating factor support:5 mcg/kg SC	Day 1 Day 1 Day 8 Day 8 Day 8 Days 3-6 and 10-13
TP/TE₸ **(Repeat every 2 weeks)**	Paclitaxel 135 mg/m^2 IV infusion Cisplatin 60 mg/m^2 IV infusion Paclitaxel 135 mg/m^2 IV infusion Etoposide 150 mg/m^2 IV infusion	Day 1 Day 1 Day 15 Day 15
ICE **(Repeat every 3 weeks)**	Ifosfamide 5000 mg/m^2 IV infusion Mesna 120 mg/m2/day IV bolus 15 minutes before Ifosfamide, then 1200 mg/m2/day IV infusion over 12 Carboplatin AUC5 IV infusion Etoposide 100 mg/m^2 IV infusion	Day 1-3 Day 2 Days 1−3
VIP **(Repeat every 3 weeks)**	Etoposide 75 mg/m^2/day IV over 60 minutes Ifosfamide 1200 mg/m^2/day IV over 3 hours Mesna 120 mg/m^2/day IV bolus 15 minutes before Ifosfamide, then 1200 mg/m^2/day IV infusion over 12 hours after the Ifosfamide dose on Days 1–5 Cisplatin 20 mg/m^2/day IV over 60 minutes Filgrastim 5 mcg/kg SC	Days 1-5 Days 1-5 Days 1-5 Days 6–14
BEP **(Repeat every 3 weeks)**	Bleomycin 30 units IV Etoposide 100 mg/m^2 IV infusion Cisplatin 20 mg/m2 IV infusion	Days 1,8,15 Days 1−5 Days 1−5
BEP‡ (Repeat every 3 weeks	Bleomycin 30 units IV Etoposide 165 mg/m^2 Cisplatin- 50mg/m^2	Days 1,8,15 Days 1−3 Days 1−2
Low-dose induction chemotherapy **(Weekly for 1 to 3 weeks)**	Etoposide 100 mg/m^2 IV infusion Cisplatin 20 mg/m^2 IV infusion	Days 1 and 2 Days 1 and 2

†For patients with brain metastases, increase the methotrexate infusion dose in the EP-EMA or EMA-EP protocol to 1000 mg/m2 and extend the infusion from 12 to 24 hours; give leucovorin 15 mg PO every 6 hours for 12 doses starting 32 hours after the start of the EP-EMA: Etoposide, Cisplatin/Etoposide, Methotrexate, Dactinomycin, Methotrexate infusion. EMA-EP, EP-EMA†-Both regimens are given in EMACO-resistant patients or in brain metastases due to better penetration, since the combination of etoposide and cisplatin (EP) is more potent than the cyclophosphamide and vincristine combination in EMACO. In EP-EMA, the most potent part of the regimen, cisplatin, is placed on day 1 to more aggressively target bulky or rapidly progressing tumors. The doses of etoposide and cisplatin in EP-EMA are higher than EMA-EP. Both regimens need intensive hydration and anti-emetic management. There are also more myelosuppression (etoposide) and nephrotoxicity (cisplatin) side effects.
TP/TE₸-One may give carboplatin instead of cisplatin in reduced kidney function. BEP‡-modified regimen for a shorter hospital stay.

Premedication before administration of chemotherapeutic agents

Patients with Gestational Trophoblastic Neoplasia require premedication (30 to 60 minutes) before chemotherapy to prevent drug adverse effects such as nausea, vomiting, and allergic reactions as indicated in Table 47.

Table 47. GOSK recommendations for premedication regimen for administration before chemotherapeutic agents

Drug class	GOSK recommendations			
	Examples	**Typical dose**	**Route**	**Indication**
5-HT3 antagonists	Ondansetron Granisetron Palonosetron†	8-16 mg 1 mg 2 mg 0.25mg	IV IV PO IV or PO	Prevent acute nausea and vomiting
Corticosteroids	Dexamethasone	12 mg 8 mg	IV or PO Day 1 IV or PO daily for 2- 4 days (high-risk regimens)	Enhances antiemetic effect, reduces inflammation
Antihistamines	Chlorpheniramine	10mg	IV	Prevents allergic reactions
Proton pump inhibitors	Esomeprazole	40 mg	IV	Prevents mucosal ulceration
IV: intravenous, PO: per oral, †: palonosetron is preferred for its long-term effects, especially in drugs that are highly emetogenic and have delayed vomiting such as cisplatin.				

Table 48. GOSK recommendations on additional agents and regimens for treating multiagent chemotherapy-resistant GTN

GOSK recommendations	
Regimen	**Drug, dosage, route, and administration**
PD-1/PD-L1 inhibitors	• Pembrolizumab 200 mg IV over 30 minutes every 3 weeks or 400 mg IV over 30 minutes every 6 weeks • Nivolumab 240 mg IV over 30 minutes every 2 weeks or 480 mg IV over 30 minutes every 4 weeks • Avelumab 800 mg IV over 60 minutes every 2 weeks • Nivolumab + ipilimumab Nivolumab 240 mg IV every 2 weeks Ipilimumab 1 mg/kg IV every 6 weeks
Vascular endothelial growth factor (VEGF) inhibitor- **Bevacizumab**	• Bevacizumab 10-15mg/kg every two weeks in combination with EMA-EP. No bevacizumab maintenance.
Capecitabine-based regimens (Repeat cycle every 3 weeks)	Capecitabine 1250 mg/m^2 PO twice daily for 2 weeks on and 1 week off
Gemcitabine ± cisplatin (Repeat every 4 weeks)	Gemcitabine 600–800 mg/m^2/day IV over 30 minutes on Days 1, 8, and 15 Cisplatin 25–30 mg/m^2/day IV over 60 minutes on Days 1, 8, and 15
High-dose chemotherapy with peripheral hematopoietic cell transplant (HCT)	
PD-1: programmed cell death protein 1, PD-L1: Programmed death ligand 1	

Radiotherapy in GTN

Radiotherapy is an important modality of treatment of patients with Gestational Trophoblastic Neoplasia as outlined in Table 49.

Table 49. GOSK recommendations for radiotherapy in GTN

GOSK recommendations	
Treatment modality	**Dosage**
Whole Brain Radiation Therapy Preferred treatment for: • Extensive intracranial disease (diffuse brain metastases≥5) • Patients with good/intermediate prognosis who are not candidates for Stereotactic Radiosurgery (SRS) or surgery	Recommended standard whole-brain radiation dosage: • 30 Gray in 10 fractions or 37.5 Gray in 15 fractions Manage side effects of radiation to include: ➢ Nausea and vomiting Premedication with 24 mg of dexamethasone BID, ondansetron 4mg QID ➢ Neurocognitive deficits Memantine 10mg daily for week 1, followed by 10 mg BID for 6 months. Administer a shorter fractionation scheme for patients with poor performance status and/or uncontrolled extracranial disease burden as follows: • 20 Gray in 5 fractions
Stereotactic Radiosurgery (SRS) • Indicated for	Administer dose depending on volume of brain lesion (cubic centimeter, cc) as follows:

GOSK recommendations	
Treatment modality	**Dosage**
• Surgically inaccessible location. • Patients who are not medically fit for surgery. • Multiple small metastatic lesions.	• <4.2 cc= 20-24 Gray • < 4.2-7.9 cc= 18 Gray • > 8.0 cc, up to 4 cm diameter=15 Gray
Hemostatic Radiotherapy in pelvic hemorrhage in GTN	Administer hemostatic pelvic radiation as follows: • 30 Gray in 10 fractions • or 20 Gray in 5 fractions • Or 8 G in one fraction.

Management of adverse effects of chemotherapy for GTN

Adverse effects of drugs are often encountered in the management of GTN. The adverse effects are outlined in Table 50. In addition, the grading of the adverse effects as developed by the National Cancer Institute is shown in Table 51.

Table 50. GOSK recommendations for management of adverse effects of chemotherapy for GTN

Adverse effects	**GOSK recommendations**	
	Drugs	**Management**
Gastrointestinal toxicity		
Nausea and vomiting	Cyclophosphamide, methotrexate, etoposide, vincristine, Cisplatin, actinomycin D	Premedication with antiemetic agents, hydration
Mucositis	Methotrexate, actinomycin D, cyclophosphamide	Cleansing agents, lubricating agents, and analgesic agents
Diarrhea	Methotrexate	Hydration, pharmacological management
Hematological toxicity		
Myelosuppression, anemia, neutropenia, thrombocytopenia	Cyclophosphamide, methotrexate, etoposide, vincristine, Cisplatin, actinomycin D	Baseline complete blood count Blood transfusion Monitor for infection, monitor for fever Dose modification Granulocyte-stimulating therapy Erythrocyte-stimulating therapy Platelet-stimulating Therapy
Dermatological toxicity		
Alopecia	Cyclophosphamide, methotrexate, etoposide, vincristine, and actinomycin D	Counselling, wear caps, hair grows 10 to 20 days after the end of treatment
Skin necrosis and sloughing due to drug extravasation	Actinomycin D	Removal of the IV line and local infiltration with Corticosteroids; use ice packs
Hypersensitivity reactions	Cyclophosphamide, cisplatin, etoposide	Premedication: corticosteroids, antihistamines; emergency drugs always available. If it occurs, stop the drug; assess airway, breathing, circulation.
Hepatic toxicity		
	Methotrexate, cyclophosphamide,	Baseline liver function tests, discontinue drugs, and drug adjustment
Pulmonary toxicity		
Interstitial pneumonitis with pulmonary fibrosis	Bleomycin	Baseline lung function tests, in case of toxicity, stop the drug, treat with steroids, and give supportive care, including oxygen
Renal Toxicity		
	Cisplatin	Baseline renal function tests, alternate drugs, in case of toxicity, use amifostine
Genitourinary Toxicity		
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide	Vigorous hydration and diuresis, a Foley catheter, for immediate drainage of the bladder. Mesna is used in conjunction with cyclophosphamide or Ifosfamide
Neurologic Toxicity		
Painful paresthesia or numbness in stocking-glove distribution	Platinum compounds: cisplatin, Carboplatin, taxanes	Avoid exposure to heat sources Alleviating compounds: vitamin E, glutamine

Adverse effects	GOSK recommendations	
	Drugs	**Management**
Metabolic Abnormality -Tumor Lysis Syndrome	Multi-agent chemotherapy for GTN if used in high tumor burden (ultra-high risk GTN)	Low-dose induction with cisplatin and etoposide before multi-agent chemotherapy in ultra-high risk GTN Hydration, correction of electrolytes

Table 51. GOSK recommendations for common terminology criteria for adverse events and the Recommended Management

Grade	Description	GOSK recommendations
Grade 1	Mild toxicity Asymptomatic or mild symptoms	Reassurance, observation only. No intervention needed
Grade 2	Moderate toxicity Minimal or local effects	Non-invasive intervention needed
Grade 3	Severe toxicity Medically significant but not life-threatening	Hospitalization needed
Grade 4	Life-threatening toxicity Disabling, potentially life-threatening	Urgent hospitalization and care needed
Grade 5	Death related to adverse effects	Appropriate explanation to next of kin. Address possible gaps
Common Terminology Criteria for Adverse Events (CTCAE) V.6, National Cancer Institute, National Institutes of Health[19]*.*		

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