National Cancer Control Programme

Diagnosis, staging and treatment of patients with gestational trophoblastic disease

National Clinical Guideline
May 2022

Guideline Development Group

The National Clinical Guideline on the diagnosis, staging and treatment of patients with gestational trophoblastic disease (GTD) in Ireland has been developed by the National Cancer Control Programme (NCCP), in collaboration with clinicians, patient representatives, librarians and stakeholdergroups.

Using this National Clinical Guideline

This National Clinical Guideline applies to all teenagers and adults that have a suspected diagnosis of Gestational Trophoblastic Disease (GTD). This guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with GTD.

While the Chief Executive Officer (CEO), General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

This guideline is also relevant to those involved in clinical governance, in both primary and secondary care, to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients with GTD and their significant others.

A list of medical abbreviations used throughout the guideline can be found in Appendix VIII: Glossary of terms and abbreviations.

Disclaimer

'This guideline ("the Guideline") was developed by a multidisciplinary Guideline Development Group ("the Group") and is based upon the best clinical evidence available together with the clinical expertise of the Group members. The Guideline supersedes all previous Health Service Executive (HSE), National Cancer Control Programme (NCCP) and National Clinical Effectiveness Committee (NCEC) guidelines for gestational trophoblastic disease. The NCCP is part of the HSE and any reference in this disclaimer to the NCCP is intended to include the HSE. Please note, the Guideline is for guidance purposes only. The appropriate application and correct use of the Guideline is the responsibility of each health professional.

The Guideline Development Group's expectation is that health professionals will use clinical knowledge and judgment in applying the principles and recommendations contained in this guideline.

These recommendations may not be appropriate in all circumstances and it may be necessary to deviate from this guideline. Clinical judgment in such a decision must be clearly documented. Care options should be discussed with the patient, his/her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary.

The NCCP accepts no liability nor shall it be liable, whether arising directly or indirectly, to the user or any other third party for any claims, loss or damage resulting from any use of the Guideline'.

Membership of the Guideline Development Group

The Co-Chairs of the Guideline Development Group were Dr John Coulter, Consultant Obstetrician and Gynaecologist, Clinical Lead of the National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre, and Dr Eve O'Toole, Head of the Evidence and Quality Hub, NCCP. This National Clinical Guideline is supported by the NCCP.

Membership nominations were sought from a variety of clinical and non-clinical backgrounds so as to be representative of all key stakeholders within the Health Service Executive. Guideline Development Group members included patient representatives, those involved in clinical practice, hospital administration, project management, and research and librarian services.

The NCCP would like to acknowledge the guideline development group responsible for the development of 'National Clinical Guideline No. 13 Diagnosis, staging and treatment of patients with gestational trophoblastic disease' in 2015, on which this guideline is based.

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Acknowledgments

The Co-Chairs of the Guideline Development Group Dr John Coulter and Dr Eve O'Toole wish to acknowledge all members of the Guideline Development Group as full contributors credited with having given substantial intellectual leadership to the National Clinical Guideline. The Chairs are especially grateful to the patient representatives for their valuable contribution to the National Clinical Guideline.

The Guideline Development Group clinical members, methodology chair, research members and project manager agreed the scope of the update and reviewed and updated the clinical questions. The Guideline Development Group librarians and research members carried out the systematic searches for evidence. The Guideline Development Group research members reviewed the evidence, appraised the literature and performed the data extraction. The Guideline Development Group led by Dr Eve O'Toole carried out the evidence synthesis including formulation of the evidence summaries and recommendations.

Ms Catherine Duffy and Ms Louise Murphy conducted the budget impact analysis. Ms Caroline Joyce and Dr Seán Costelloe developed a business case on the establishment of a National hCG diagnostic service. Ms Catherine Duffy and Ms Louise Murphy prepared the implementation plan in collaboration with relevant stakeholders. All authors approved the final guideline.

The external review carried out by Professor Michael Seckl, Charing Cross Hospital is acknowledged and greatly appreciated.

We would like in addition to thank Ms Louise Murphy for her editorial support during preparation for publication.

A full list of members of the Guideline Development Group is available in the previous page/s.

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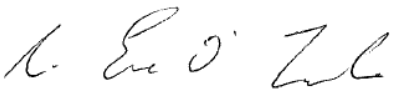

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1.0 Background

1.1 Impact of Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) is a spectrum of diseases that can occur during or after pregnancy, each having a varying propensity for local invasion and metastasis. GTD has been defined as a continuum of a neoplastic process that arises from the trophoblastic cells that during pregnancy are involved in the development of the placenta. Its pathogenesis is unique as it arises from gestational rather than maternal tissue (Berkowitz et al., 2020). The World Health Organisation (WHO) has classified GTD as two premalignant diseases, consisting of complete hydatidiform mole (CHM) and partial hydatidiform mole (PHM), and as four malignant disorders, consisting of invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). The last four conditions are often collectively referred to as gestational trophoblastic neoplasia (GTN) (Kumar & Kumar, 2011).

GTD is the most curable of all gynaecologic malignancies. It represents an oncologic success story attributable primarily to early disease recognition, chemotherapy regimens, and accurate and reliable assessment of disease status with sensitive assays for the measurement of human chorionic gonadotropin (hCG) levels.

Its importance as a disease status cannot be overstated to the general gynaecologist, who is initially responsible for the diagnosis and management of GTD as well as the timely registration of the patient at the National Gestational Trophoblastic Disease Registry, Monitoring & Advisory Centre and referral to a gynaecological oncologist. The management of these women is specialised and, in many countries, is undertaken by gynaecological and medical oncologists with special expertise in treating this disease. A structured approach to diagnosis and management will result in a cure for most patients, even in the setting of advanced disease, without adversely affecting future fertility (McGee & Covens, 2012).

1.2 National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre

The National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre was established in May 2017 to monitor and co-ordinate the follow-up of women who have been diagnosed with a molar pregnancy. It is a service established by the Health Service Executive (HSE), the NCCP and Cork University Maternity Hospital (CUMH) and is the only such centre in Ireland. GTD is a rare disease, and registration of all patients with GTD is recommended as a minimum standard of care. The GTD centre provides monitoring and advice to patients and clinicians on the care of patients with GTD.

The outcome for more than 98% of women with GTN is excellent however a small number of women will die from the disease, mainly due to late presentation and diagnosis or drug resistance (Seckl et al., 2010). The latest figures indicate that in 2021, 138 women with suspected GTD were registered with the National Gestational Trophoblastic Disease Registry, Monitoring & Advisory Centre. As not all patients are currently registered with the GTD centre this underestimates the incidence of this disease. A 2019 laboratory study estimated that 42% of women with suspected GTD/GTN were not registered with the National Gestational Trophoblastic Disease Registry, Monitoring & Advisory Centre. This highlights the need to reinforce the importance of registering all patients, with suspected or confirmed GTD, going forward.

1.3 Context and Scope of this National Clinical Guideline

This guideline aims to improve the standard of clinical practice to ensure that women affected by GTD and GTN are diagnosed promptly and receive the best available treatment and care.

The diagnosis, staging, and treatment of patients with GTN requires multidisciplinary care in an acute hospital setting. The majority of patients will require diagnostic tests (radiology, pathology) and depending on the treatment plan may require surgery and chemotherapy.

2.0 National Clinical Guideline

2.1 Summary of Clinical Questions and Recommendations

Here follows a list of all the recommendations in this guideline, along with the quality of evidence and strength of each recommendation. The quality of evidence and strength of recommendation system used is defined in Appendix X: Levels of evidence and grading systems. All terms and abbreviations used in the recommendations can be found in Appendix VIII: Glossary of terms and abbreviations.

Clinical question 2.2.1

Should all women undergoing medical management of miscarriage have histopathology of products of conception to exclude trophoblastic disease?

Recommendation 2.2.1.1: The histological assessment of material obtained from the surgical management of all failed pregnancies is recommended to exclude trophoblastic disease.

Quality of Evidence: Low **Grade of recommendation:** Strong

Recommendation 2.2.1.2: All women undergoing medical management of miscarriage or medical termination of pregnancy should be advised to perform a follow-up urinary pregnancy test two to four weeks after miscarriage/termination.

Quality of Evidence: Very low **Grade of recommendation:** Strong

Good Practice Point: In women undergoing a miscarriage, communication should be sensitive and in line with local hospital policy.

Practical considerations around patient care:

- The patient should be provided with relevant information (e.g. a leaflet) explaining why the sample is sent to the laboratory.

Clinical question 2.2.2

For women with suspected molar pregnancy (suspected partial hydatidifrom mole [PHM], complete hydatidifrom mole [CHM] or in patients where molar pregnancy cannot be excluded), what diagnostic tests should be done to accurately diagnose partial or complete molar pregnancy?

Recommendation 2.2.2.1: Ultrasound examination can be helpful in the pre-evacuation suspicion of complete molar pregnancy but the definitive diagnosis is made by histological examination of the products of conception.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Recommendation 2.2.2.2: Laboratories examining products of conception should have access to p57KIP2 immunohistochemistry to aid in the differential diagnosis of complete, partial or non-molar pregnancies.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Good Practice Point: GTD may be diagnosed in the absence of histopathological proof based on clinical, radiological, or biochemical suspicion (raised hCG). In these circumstances early expert referral to the National GTD Registry, Monitoring and Advisory Centre is recommended.

Practical considerations around patient care:

- All patients registered with the National GTD Registry, Monitoring and Advisory Centre should have access to a specialist nurse for information, counselling and support.
- Written information, guidance and support for health professionals and GPs should be available including a link to the National GTD Registry, Monitoring and Advisory Centre website.

Clinical question 2.2.3

For women where there is suspicion of partial or complete molar pregnancy who have an evacuation performed, in what time frame should the pathology report (post-evacuation) be available to the clinician?

Recommendation 2.2.3.1: In cases of suspected molar pregnancy, a pathology report should be available to the clinician within 14 calendar days.

Quality of Evidence: Very low **Grade of recommendation:** Weak

Recommendation 2.2.3.2: If molar pregnancy is suspected the requesting clinician should indicate their clinical suspicion on the pathology request form and/or inform the pathologist.

Quality of Evidence: Very low **Grade of recommendation:** Weak

Good Practice Point

GTD may be diagnosed in the absence of histopathological proof based on clinical, radiological, or biochemical suspicion (raised hCG). In these circumstances early expert referral to the National GTD Registry, Monitoring and Advisory Centre is recommended.

In certain cases where ancillary laboratory testing is needed additional time may be necessary for a diagnosis.

Written information, guidance and support on GTD for health professionals including GPs should be available including a link to the National GTD centre website

Practical considerations around patient care

- Patients should be informed that results from the pathology test will take two weeks.
- Patients with a suspected complete hydatidiform mole should be offered a follow-up appointment two weeks from the date of evacuation.
- In patients where a complete hydatidiform mole is suspected on ultrasound, the patient should be informed and counselled of the suspected diagnosis and the follow-up that may be required.
- Clinicians and patients should refer to the following website for information: https://irelandsouthwid.cumh.hse.ie/gynaecology/gtd-centre/about-gtd-centre/

Clinical question 2.2.4

Which patients with confirmed or suspected GTD should be registered with the National GTD Registry, Monitoring and Advisory Centre?

Recommendation 2.2.4.1: The guideline development group recommends that all women with suspected GTD should be registered with the National GTD Registry, Monitoring and Advisory Centre.

Quality of Evidence: Very low **Grade of recommendation:** Strong

Good Practice Point
The registration of women with suspected GTD with the National GTD Registry, Monitoring and Advisory Centre represents a minimum standard of care.

Clinical question 2.2.5

In patients with suspected GTD, how should human chorionic gonadotropin (hCG) be measured?

Recommendation 2.2.5.1: hCG serum should be measured using an assay that is CE marked for oncology.

Quality of Evidence: Low **Grade of recommendation:** Strong

Good Practice Point
The registration of women with suspected GTD with the National GTD Registry, Monitoring and Advisory Centre represents a minimum standard of care.

hCG testing should be performed in a laboratory that is accredited to medical testing standard ISO 15189 (2012).

Clinical question 2.2.6

For women with partial and complete molar pregnancy, what clinical and hCG monitoring protocol should be carried out to ensure they have been fully followed up and require no further therapy or monitoring?

Recommendation 2.2.6.1: For patients with complete hydatidiform mole, serum hCG is monitored weekly (on the same platform) until normalisation is achieved for three weeks.

- If this occurs within eight weeks post evacuation then monitor monthly for six months from the time of evacuation.
- If normalisation occurs greater than eight weeks post evacuation then monitoring continues monthly for six months post normalisation.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Recommendation 2.2.6.2: For patients with partial hydatidiform mole, serum hCG should be monitored weekly (on the same platform) until normalisation and one further confirmatory hCG measurement should be performed four weeks later. If that confirmatory hCG is normal then follow-up is complete.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Good Practice Point
For all women with a previous diagnosis of GTD, early fetal ultrasound is standard practice to ensure a normal intrauterine pregnancy and to rule out recurrence of a molar pregnancy.

If a normal intrauterine pregnancy is confirmed there are no extra investigations necessary during the pregnancy.

Serum hCG should be monitored on an assay that is CE marked for use in oncology (please refer to clinical question 2.2.5 for more information).

Clinical question 2.2.7

In women with confirmed GTD should monitoring of hCG be centralised?

Recommendation 2.2.7.1: hCG testing should be centralised in women with confirmed GTD who have been registered with the National GTD Registry, Monitoring and Advisory Centre.

Quality of Evidence: Very Low **Grade of recommendation:** Strong

Good Practice Point

The registration of women with suspected GTD with the National GTD Registry, Monitoring and Advisory Centre represents a minimum standard of care.

Clinical question 2.3.1

For women with Gestational Trophoblastic Neoplasia (GTN), what investigations should be done to accurately stage GTN?

Recommendation 2.3.1.1: Women with a diagnosis of GTN should have serum hCG monitoring, ultrasound and a CT scan of thorax, abdomen & pelvis performed within one week of diagnosis.

Quality of Evidence: Low **Grade of recommendation:** Strong

Recommendation 2.3.1.2: If clinically significant lung metastases are present on a CT scan of the thorax a contrast enhanced MRI of the brain should be performed.

Quality of Evidence: Low **Grade of recommendation:** Strong

Good Practice Point: Investigation and management decisions should be performed by experienced professionals in the management of GTD.

Practical considerations around patient care

- Patients should be counselled and reassured of the high cure rate of this patient cohort.

Clinical question 2.3.2

For women with GTN, what risk scoring system should be used to stage GTN?
[Retained from 2015]

Recommendation 2.3.2.1: Women with GTN (invasive mole, choriocarcinoma) should be assigned a FIGO score to direct management decisions of chemotherapy regimens.

Grade of recommendation: Grade B

Good Practice Point: Placental site trophoblastic tumour and epithelioid trophoblastic tumour should not be scored using the FIGO system. They require separate classification in consultation with international experts.

Clinical question 2.4.1

For women with GTN, what are the clinical indicators to diagnose GTN warranting chemotherapy?

Recommendation 2.4.1.1: Indications for chemotherapy following diagnosis of GTN:
• Plateaued or rising hCG after evacuation,

• Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage,
• Histological evidence of choriocarcinoma, except in exceptional circumstances,
• Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities of >2cm on chest x-ray.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Recommendation 2.4.1.2: Women who have a raised hCG six months after evacuation with a falling hCG should have their treatment plan discussed with the National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre.

Quality of Evidence: Low **Grade of recommendation:** Strong

Recommendation 2.4.1.3: Women with serum hCG of ≥20,000 IU/L more than four weeks after evacuation should have their treatment plan discussed with the National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre.

Quality of Evidence: Low **Grade of recommendation:** Strong

Good Practice Point
For women with histological evidence of choriocarcinoma primary surgery may be considered.

The treating physician should ensure that the patient is registered with the National GTD Registry, Monitoring and Advisory Centre.

Clinical question 2.4.2

For patients with low-risk (FIGO 0-6) GTN, what is the optimal first-line chemotherapy regimen?

Recommendation 2.4.2.1: Patients with a FIGO score of 0-6 can be treated with either single-agent methotrexate with or without folinic acid, or actinomycin D. Taking into account the treatment cycles, potential complications and quality of life the guideline development group agreed that the IM methotrexate 8 day regimen is the preferred first-line chemotherapy.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Recommendation 2.4.2.2: Chemotherapy for low-risk disease should be continued for three cycles of consolidation treatment at the standard two weekly cycle after hCG normalisation.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Good Practice Point
In patients with low risk GTN serum hCG/blood should be measured prior to each chemotherapy cycle or more frequently if required.

Practical considerations around patient care

- Patients diagnosed with GTN should have access to counselling and support from the nurses in the National GTD Registry, Monitoring and Advisory Centre.
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- Patients diagnosed with GTN should have access to a liasion nurse or designated key contact in the patient's treatment centre who should also be in contact with the National GTD Registry, Monitoring and Advisory Centre.

Clinical question 2.4.3

For women with high-risk (FIGO ≥7) GTN, what is the optimal first-line chemotherapy regimen?

Recommendation 2.4.3.1: Patients with a FIGO score of ≥7 should receive multi-agent chemotherapy and most centres now use EMA/CO, as it is highly effective.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Recommendation 2.4.3.2: Early deaths in ultra-high-risk GTN (FIGO score >12) can be reduced by induction therapy with low dose etoposide and cisplatin. Such patients may also benefit from substitution of EMA/CO with EMA/EP.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Good Practice Point

For women with high-risk GTN, decisions should be made on an individual patient basis following discussion with clinicians experienced in high-risk GTN management at a GTD Centre.

Registration of patients at the National GTD Registry, Monitoring and Advisory Centre is a minimum standard of care.

Practical considerations around patient care

- Patients should be informed that their treatment will require in-patient care.
- Patients with high-risk GTN (FIGO score of ≥7) should have access to a liaison nurse or designated key contact locally who is in contact with the National GTD Registry, Monitoring and Advisory Centre.
- Patients diagnosed with GTN should have access to a liaison nurse or designated key contact in the patient's treatment centre who should also be in contact with the National GTD Registry, Monitoring and Advisory Centre.

Clinical question 2.4.4

For women with low-risk GTN undergoing chemotherapy (first-course), what is the recommended course of action for observing and managing bleeding?
[Retained from 2015]

Recommendation 2.4.4.1: For women with low-risk GTN undergoing first-line chemotherapy, the first ± second courses of chemotherapy should be administered as an in-patient at a centre with medical oncology, gynaecological services and interventional radiology.

Grade of recommendation: Grade C

Clinical question 2.4.5

For women with GTN, what are the appropriate investigations to monitor response to chemotherapy and follow-up?

Recommendation 2.4.5.1:
Monitoring during treatment in patients with low-risk GTN:
Patient should have hCG levels measured prior to their next chemotherapy cycle. Treatment is continued until hCG is normal and for three further consolidation cycles.

Quality of Evidence: Low **Grade of recommendation:** Strong

Recommendation 2.4.5.2:
Monitoring during treatment in patients with high-risk GTN:
Patient should have hCG levels measured prior to their next chemotherapy cycle. Patients with high-risk disease should have consolidation therapy for three cycles after hCG normalisation extended to four cycles for patients with poor prognostic features such as liver metastases with or without brain metastases.

Quality of Evidence: Low **Grade of recommendation:** Strong

Recommendation 2.4.5.3:
Follow-up post treatment:
After remission is achieved, serum hCG should be measured fortnightly for six months then monthly for a further six months and every two months for two years.

Quality of Evidence: Moderate **Grade of recommendation:** Strong

Practical considerations around patient care

- Patients should have access to a nurse or designated key contact with experience treating GTN that can provide advice, written information and support to patients before commencing treatment.
- Patients should be provided with clear written information in patient-friendly language that they can share with family.

Clinical question 2.4.6

For women with gestational trophoblastic neoplasia what are the indicators to determine switching treatments from first-line chemotherapy?
[Retained from 2015]

Recommendation 2.4.6.1: For patients with low-risk GTN the clinical indicators for a change in treatment from first-line chemotherapy include: treatment related toxicity, a rise in hCG values over two successive measurements a week apart or a plateau in three successive weekly measurements a week apart.

Grade of recommendation: Grade C

Good Practice Point
Consideration could be given to re-staging patients prior to the initiation of a new regimen (particularly high-risk patients).

Clinical question 2.4.7

For women with low-risk gestational trophoblastic neoplasia who have not responded or have relapsed from single agent treatment (methotrexate or actinomycin D) or have relapsed following normalisation of hCG after completion of single agent treatment, what is the next line treatment?

Recommendation 2.4.7.1: For women with low-risk GTN who have not responded to methotrexate with a hCG <1,000 IU/L the next line of treatment is actinomycin D.

Quality of Evidence: Low **Grade of recommendation:** Strong

Recommendation 2.4.7.2: For women with low-risk GTN who have not responded to methotrexate

with a hCG >1,000 IU/L the next line of treatment is EMA/CO.

Quality of Evidence: Low **Grade of recommendation:** Strong

Recommendation 2.4.7.3: For women with low-risk GTN who have not responded or have relapsed from sequential single-agent treatment the next line of treatment is combination chemotherapy with EMA/CO.

Quality of Evidence: Low **Grade of recommendation:** Strong

Good Practice Point
Once normalistion of hCG has occurred on EMA/CO treatment etoposide can be discontinued from the regimen to reduce the risk of secondary malignancies.

Clinical question 2.4.8

For women with high-risk GTN who have not responded to first-line treatment, what is second-line treatment?

Recommendation 2.4.8.1: For women with high-risk GTN who have not responded to first-line treatment, second-line treatment is EMA/EP or TE/TP.

Quality of Evidence: Low **Grade of recommendation:** Strong

Recommendation 2.4.8.2: In women with high-risk GTN who have not responded to first-line treatment, discussions of each individual case at a GTD MDM should be considered.

Quality of Evidence: Very Low **Grade of recommendation:** Strong

Good Practice Point
All women with GTN should be registered at the National GTD Registry, Monitoring and Advisory Centre.

Given the rarity of this condition consideration should be given to discussing each individual case with international experts.

Clinical question 2.4.9

For women with GTN, who are acutely ill with liver, brain or lung metastasis at presentation, what is the optimum chemotherapy regimen?

Recommendation 2.4.9.1:
Emergency treatment
Patients who are acutely unwell from liver or CNS disease and particularly those with large lung metastases who are at risk of respiratory failure should be admitted and emergency chemotherapy commenced as soon as possible.

Quality of Evidence: Very Low **Grade of recommendation:** Strong

Recommendation 2.4.9.2:
Hepatic metastases
Patients with hepatic metastases at presentation should continue therapy using EMA/EP protocol.

Quality of Evidence: Very Low **Grade of recommendation:** Strong

Recommendation 2.4.9.3:
Cerebral metastases
Patients with cerebral metastases should be treated with EMA(CNS)/CO.

Quality of Evidence: Very Low **Grade of recommendation:** Strong

Recommendation 2.4.9.4:
Hepatic and synchronous cerebral metastases
Patients with liver and brain metastases should be treated with a combination of EMA (CNS) and EP.

Quality of Evidence: Very Low **Grade of recommendation:** Strong

Practical considerations around patient care

- Patients should be provided with reassurance that they are being managed in co-operation with the National GTD Registry, Monitoring and Advisory Centre.
- Patients should be counselled and reassured of the high cure rate of this patient cohort.

2.2 Diagnosis

The following are responsible for the implementation of the recommendations regarding diagnosis:
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.2.1

Should all women undergoing medical management of miscarriage have histopathology of products of conception to exclude trophoblastic disease?

Quality of evidence

The evidence to address this question comes from an international guideline (Tidy et al., 2020).

Surgical management of miscarriage

Histopathology of products of conception should be performed in all cases of surgical management of miscarriage (Tidy et al., 2020). Histopathology of products of conception enables earlier accurate diagnosis of trophoblastic disease.

Medical management of failed pregnancy, miscarriage or termination

Women who miscarry at home following medical termination of pregnancy or medical management of failed pregnancy should be advised to perform a follow-up urinary pregnancy test two to four weeks after miscarriage/termination as per local protocol (Tidy et al., 2020). Alternatively, they may be advised to return for an ultrasound based on clinical presentation as per local protocol. If tissue is available the attending practitioner should arrange for the appropriate examination.

Benefit and Harm

Surgical management of miscarriage

The guideline development group agreed that in all cases of surgical management of miscarriage histopathological testing of products of conception would benefit patients as it would identify trophoblastic disease if present.

Medical management of failed pregnancy, miscarriage or termination

In women who miscarry at home it was agreed that histopathological testing of products of conception had the potential to distress patients as retrieving and transferring the products of conception may cause emotional and psychological distress to the patient and the quality of the tissue sample may be poor.

The guideline development group estimate that the risk of missing a molar pregnancy that requires treatment from not having tissue for histopathology is ~ 1 in 9,000. This is based on the number of miscarriages, molar pregnancies and the number of molar pregnancies that require treatment. Therefore the benefit of having tissue is outweighed by the psychological stress that may be caused to the patient.

However, in women who undergo medical management of miscarriage who miscarry at home a follow-up urinary pregnancy test would benefit patients as it would ensure that a complete miscarriage has taken place and in patients where a complete miscarriage has not taken place further investigations are needed.

Preferences and values

Surgical management of miscarriage

The guideline development group which included patient representatives considered that for patients undergoing surgical management of miscarriage the patient is going through the emotional distress of a miscarriage and the issue of processing tissue samples should be dealt with in a sensitive manner. The patient should be counselled around why histopathology is required.

Medical management of failed pregnancy, miscarriage or termination

The guideline development group which included patient representatives considered the emotional distress of a miscarriage and agreed that the benefit of having tissue for histology is outweighed by the psychological distress and dignity of the women.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question.

The following resources and other considerations were discussed in detail by the guideline development group:

Access to histopathological assessment

In addition to routine pathological resourcing, access to specialised pathological investigations may be required in certain cases e.g. P57KIP2 immunohistochemistry/ploidy assessment/molecular analysis. These requirements are detailed further in Clinical question 2.2.2.

Recommendation 2.2.1.1:

The histological assessment of material obtained from the surgical management of all failed pregnancies is recommended to exclude trophoblastic disease.

Quality of Evidence: Low **Grade of recommendation: Strong**

Recommendation 2.2.1.2:

All women undergoing medical management of miscarriage or medical termination of pregnancy should be advised to perform a follow-up urinary pregnancy test two to four weeks after miscarriage/termination.

Quality of Evidence: Very low **Grade of recommendation: Strong**

Good Practice Point

In women undergoing a miscarriage, communication should be sensitive and in line with local hospital policy.

Practical considerations around patient care

- The patient should be provided with relevant information (e.g. a leaflet) explaining why the sample is sent to the laboratory.

Clinical question 2.2.2

For women with suspected molar pregnancy (suspected partial hydatidifrom mole [PHM], complete hydatidifrom mole [CHM] or in patients where molar pregnancy cannot be excluded), what diagnostic tests should be done to accurately diagnose partial or complete molar pregnancy?

Quality of evidence

There is international consensus that for women with suspected molar pregnancy further tests should be done and that histopathology is the gold standard (Tidy et al., 2020, Bolze et al., 2015, Niemann et al., 2015, ESMO - Seckl et al.,, 2013).

In the largest series of more than 1,000 consecutive patients with suspected molar pregnancy, the reported sensitivity, specificity, positive predictive value, and negative predictive value of ultrasonography were 44%, 74%, 88%, and 23%, respectively (Fowler et al., 2006).

Sebire and colleagues (2001) reported that ultrasonography accurately detected molar pregnancy in only 34% of 155 pathologically proven molar pregnancies. However, 84% of sonographically suspected cases of molar pregnancy were histopathologically proven (53 out of 63), indicating a high positive predictive value.

Therefore for women with suspected complete molar pregnancy on ultrasound histopathology should be performed and is the gold standard. For women with partial moles may not be suspected on ultrasound and the diagnosis of a partial hydatidiform mole is established by:

- Histopathological examination
- Cytogenetic and molecular biological examination if indicated.

The following may help with the suspicion of a molar pregnancy:

- History
- Clinical examination
- Ultrasound examination
- Serum hCG (human chorionic gonadotropin) levels

For laboratories examining products of conception it is recommended they have access to p57KIP2 immunohistochemistry to aid in the differential diagnosis of complete and partial molar pregnancies (Erol et al., 2016, EMSO - Seckl et al.,, 2013).

At present, genetic studies remain a useful adjunct to histopathological diagnosis in selected cases rather than routine investigation. (Sebire, 2010)

Clinicians should liaise with their local laboratory to optimise diagnosis.

Benefit and Harm

The guideline development group agreed that patients would benefit from the diagnostic tests as they would lead to the timely diagnosis and efficient management of patients with GTD.

Diagnostic tests have a potential for harm as there is a risk of false positives that may lead to unnecessary interventions, anxiety and a possible delay in trying for a subsequent pregnancy.

Preferences and values

The guideline development group which included patient representatives agree that peace of mind and trust in their diagnosis and follow-up plan is important to the patient.

Further reassurance can be provided to the patient by registering them with the National GTD Registry, Monitoring and Advisory Centre where they can be provided with consistent up to date information, support and advice.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question.

The following resources and other considerations were discussed in detail by the guideline development group:

Access to histopathological assessment

Histopathological assessment of molar pregnancy should include p57KIP2. In addition to routine pathological resourcing, access to specialised pathological investigations may be required in certain cases e.g. P57KIP2 immunohistochemistry/ploidy assessment/molecular analysis.

Serum hCG testing

hCG follow-up may have a financial implication for patients as a small number of women attend their GP for follow-up blood tests incurring personal cost. The guideline development group agreed that it would be useful for the GP to receive information along with a letter from the GTD centre regarding their patients care.

Recommendation 2.2.2.1:

Ultrasound examination can be helpful in the pre-evacuation suspicion of complete molar pregnancy but the definitive diagnosis is made by histological examination of the products of conception.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.2.2.2:

Laboratories examining products of conception should have access to p57KIP2 immunohistochemistry to aid in the differential diagnosis of complete, partial or non-molar pregnancies.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Good Practice Point

GTD may be diagnosed in the absence of histopathological proof based on clinical, radiological, or biochemical suspicion (raised hCG). In these circumstances early expert referral to the National GTD Registry, Monitoring and Advisory Centre is recommended.

Practical considerations around patient care

- All patients registered with the National GTD Registry, Monitoring and Advisory Centre should have access to a specialist nurse for information, counselling and support.
- Written information, guidance and support for health professionals and GPs should be available including a link to the National GTD Registry, Monitoring and Advisory Centre website.

Clinical question 2.2.3

For women where there is suspicion of partial or complete molar pregnancy who have an evacuation performed, in what time frame should the pathology report (post-evacuation) be available to the clinician?

Quality of evidence

The evidence that informs this question comes from the fact that most women who develop persistent GTD do so within 12 weeks of evacuation (Soto-Wright et al., 1995).

Soto-Wright et al. (1995) and Sun et al. (2015) observed that the diagnosis of complete hydatidiform mole was being made earlier in gestation, the median gestational age of complete molar pregnancy at the time of evacuation was reduced from 16 weeks (1965 -1975) to 12 weeks (1988 -1993) to 9 weeks (1994-2013). The use of ultrasound in early pregnancy has probably led to the earlier diagnosis of molar pregnancy.

Some women present acutely unwell and require chemotherapy less than two weeks post evacuation. Laboratory tests should be prioritised by histopathology departments attached to maternity hospitals in cases of suspected GTD.

If complete molar pregnancy is suspected on ultrasound the pathology department should be informed at the time of the uterine evacuation.

Benefit and Harm

The guideline development group agreed that the timeframe of two weeks for a pathology report would benefit the patient as it would lead to an earlier confirmed diagnosis which would allow for prompt patient management.

A delay in pathology report has a potential for harm as it may cause a delay in diagnosis and treatment and an increase in patient anxiety.

Preferences and values

The guideline development group which included patient representatives agreed that a timeframe of two weeks for a pathology report provides clarity for the patient and reduces anxiety.

Communication around timeframes and the potential diagnosis are important in managing patients and clinicians expectations and maintaining trust.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question.

No barriers were identified to implementing the recommendations.

Recommendation 2.2.3.1:
In cases of suspected molar pregnancy, a pathology report should be available to the clinician within 14 calendar days.

Quality of Evidence: Very low **Grade of recommendation: Weak**

Recommendation 2.2.3.2:
If molar pregnancy is suspected the requesting clinician should indicate their clinical suspicion on the pathology request form and/or inform the pathologist.

Quality of Evidence: Very low	Grade of recommendation: Weak

Good Practice Point
GTD may be diagnosed in the absence of histopathological proof based on clinical, radiological, or biochemical suspicion (raised hCG). In these circumstances early expert referral to the National GTD Registry, Monitoring and Advisory Centre is recommended.

Good Practice Point
In certain cases where ancillary laboratory testing is needed additional time may be necessary for a diagnosis.

Good Practice Point
Written information, guidance and support on GTD for health professionals including GPs should be available including a link to the National GTD centre website

Practical considerations around patient care

- Patients should be informed that results from the pathology test will take two weeks.
- Patients with a suspected complete hydatidiform mole should be offered a follow-up appointment two weeks from the date of evacuation.
- In patients where a complete hydatidiform mole is suspected on ultrasound, the patient should be informed and counselled of the suspected diagnosis and the follow-up that may be required.
- Clinicians and patients should refer to the following website for information: https://irelandsouthwid.cumh.hse.ie/gynaecology/gtd-centre/about-gtd-centre/

Clinical question 2.2.4

Which patients with confirmed or suspected GTD should be registered with the National GTD Registry, Monitoring and Advisory Centre?

Quality of evidence

The evidence discusses the United Kingdom model of centralisation, which has led to excellent historical outcomes and ongoing improvement. The low rate of relapse and high subsequent cure rate supports a policy of informing treated patients that they are almost certainly cured (97%), but that they should take part in a structured hCG follow-up programme because of the small (3%) chance of relapse (Sita-Lumsden et al., 2012) .

This is supported by a recent worldwide survey that demonstrated that mortality for patients with GTN primarily treated at a trophoblastic centre was 2.1% (59 of 2859 patients) compared to 8% (149 of 1854 patients) among those referred after failure of primary treatment ($P < 0.001$ by X^2)(Kohorn, 2014).

A National GTD Registry, Monitoring and Advisory Centre for patients with GTD was established in Ireland in 2017 to monitor and co-ordinate care of all women in Ireland with GTD. All patients with GTD should be registered with the National GTD Centre to allow centralised monitoring of hCG levels and co-ordination of care. The National Clinical Lead will notify the patients' treating clinician if further intervention/treatment is needed following hCG monitoring.

A national histopathology audit carried out in 2019 has shown that approximately 45% of patients (32% complete hydatidiform moles, 41.2% of partial hydatidiform moles) who should be registered with the National GTD Centre had not been registered. Since going live in 2017 the National GTD Centre has managed over 500 women in Ireland with gestational trophoblastic disease and molar pregnancy with a 100% success rate. Many of these women have required multiple courses of chemotherapy but all have been cured.

Based on the Royal College of Obstetrics and Gynaecology guideline (Tidy et al., 2020) the guideline development group recommend that women with the following diagnoses should be registered and require follow-up:

- CHM
- PHM
- twin pregnancy with CHM or PHM
- limited macroscopic or microscopic molar change suggesting possible early CHM or PHM
- choriocarcinoma
- PSTT or ETT
- atypical placental site nodule
- atypical GTD suspected
- p57KIP2 discordant villi

Benefit and Harm

The guideline development group identified the following benefits of being registered at the National GTD Centre for patients:

- Standardisation and optimisation of care for women
- Emotional support is provided to patients by the centre. It re-assures patient to have a point of contact with a CNS at the National GTD Registry, Monitoring and Advisory Centre.
- The centre advocates and communicates with the treating hospital on behalf of the patient
- Reduced inequity for patients who are not being treated at the centre
- The gathering of prospective data allows treatment to be tailored to the Irish population.

The guideline development group did not identify any harm in registering the patient at the National GTD Centre.

Preferences and values

The guideline development group which included patient representatives agreed that the reassurance and understanding provided by the centre is important to the patient. All women with suspected GTD should be registered with the National GTD Centre allowing them to have equitable access to the support provided by the centre.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this question.

Designated point of contact

The guideline development group identified that each maternity hospital should have a designated point of contact/person to advocate registration of patients at the National GTD Registering, Monitoring and Advisory centre.

Recommendation 2.2.4.1:

The guideline development group recommends that all women with suspected GTD should be registered with the National GTD Registry, Monitoring and Advisory Centre.

Quality of Evidence: Very low **Grade of recommendation: Strong**

Good Practice Point

The registration of women with suspected GTD with the National GTD Registry, Monitoring and Advisory Centre represents a minimum standard of care.

Clinical question 2.2.5

In patients with suspected GTD, how should human chorionic gonadotropin (hCG) be measured?

Quality of evidence

Two retrospective studies and international guidelines addressed this clinical question (de Souza et al., 2017, Lertkhachonsuk, 2015, National Comprehensive Cancer Network (NCCN), 2021, Santaballa et al., 2018, ESMO - Seckl et al., 2013, Harvey et al., 2021).

The hCG assay used for women with GTD is different from that used in the hCG pregnancy test. To differentiate both hCG assays, the test code TM hCG should be used when measuring hCG as a tumour marker in women with GTD.

hCG serum or plasma should be tested using an assay that can detect all forms of hCG and is CE marked for use in oncology.

hCG testing should be performed in a laboratory that is accredited to medical testing standard ISO 15189 (International Organization for Standardization, 2012).

Benefit and Harm

The guideline development group identified the following benefits:

- Use of an approved hCG assay for appropriate treatment, management and follow-up of patients will facilitate standardisation of care including:
    - Facilitate the accurate monitoring of patients
    - Facilitate understanding of the impact of treatment on hCG levels
    - Inform future monitoring pathways.
- Facilitation of national audit in this cohort

The guideline development group identified the following potential harms:

- Potential for false negative or false positives

Preferences and values

The guideline development group which included patient representatives considered the use of a hCG assay that is CE marked for oncology and agreed that it would provide reassurance and certainty to patients and clinicians involved in their care.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question.

The following resources and other considerations were identified by the guideline development group:

Communication of guideline recommendations

Development of a dissemination and communication plan to ensure all women with suspected GTD are registered with the National GTD Registry, Monitoring and Advisory Centre.

Recommendation 2.2.5.1:

hCG serum should be measured using an assay that is CE marked for oncology.

Quality of Evidence: Low **Grade of recommendation: Strong**

Good Practice Point
The registration of women with suspected GTD with the National GTD Registry, Monitoring and Advisory Centre represents a minimum standard of care.

Good Practice Point
hCG testing should be performed in a laboratory that is accredited to medical testing standard ISO 15189 (2012).

Clinical question 2.2.6

For women with partial and complete molar pregnancy, what clinical and hCG monitoring protocol should be carried out to ensure they have been fully followed up and require no further therapy or monitoring?

Quality of evidence

There are a number of different protocols for the follow-up of hCG levels (Charing Cross Hospital, 2019, Bagshawe et al., 1986, Alazzam et al., 2011). If hCG levels normalise within 56 days of the uterine evacuation risk of persistent subsequent disease is almost negligible (Seckl et al., 2010, Coyle et al., 2018).

Serum hCG should be monitored on an assay that is CE marked for use in oncology. The same assay should be used consistently throughout patient follow-up. It is important to avoid switching between multiple assays or laboratories which can influence result interpretation.

Complete hydatidiform mole

For complete molar pregnancy serum hCG is monitored weekly until normalisation for three weeks. If this occurs within eight weeks then monitor monthly for six months post evacuation. If normalisation occurs more than eight weeks post evacuation the monitoring continues monthly for six months post normalisation (Figure 1). The current protocol is consistent with international best practice and is chosen for consistency.

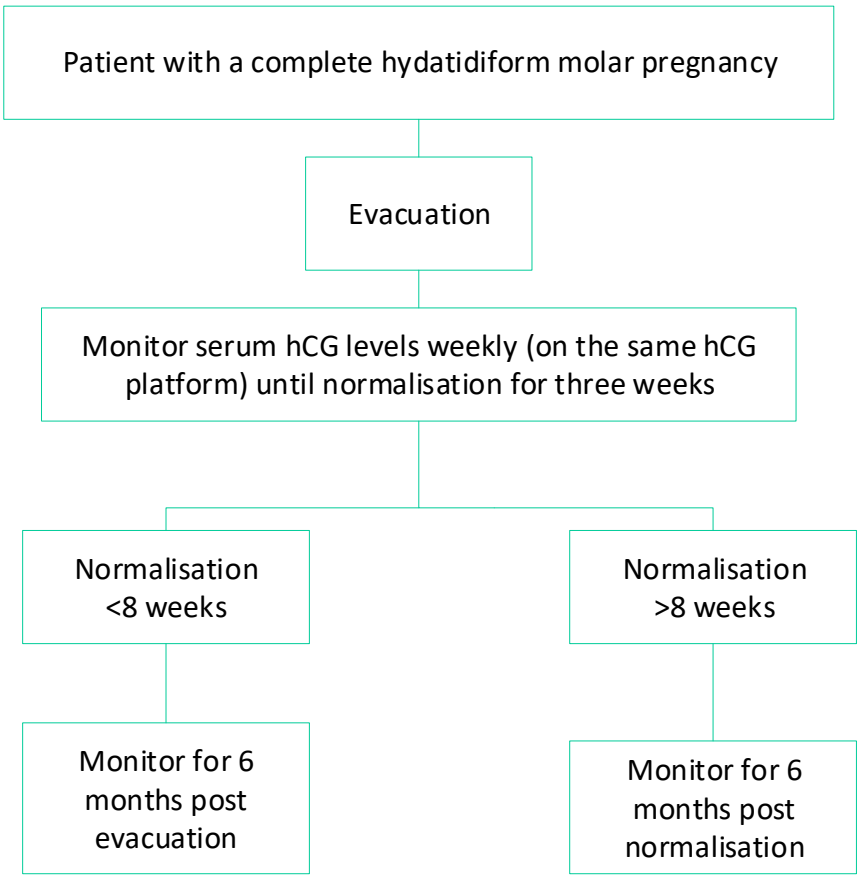


Figure 1 The current protocol for monitoring hCG levels in women with complete hydatidiform molar pregnancy

Partial hydatidiform mole

For partial hydatidiform mole, stopping hCG surveillance after normalisation in more than 500 patients did not result in GTN being missed. In a prospective cohort of 1,980 patients diagnosed pathologically with GTD, the risk of developing GTN (239 patients) in patients with a normalised hCG was shown to be 0.36% (4/1,122) for complete hydatidiform mole and 0% (0/593) for partial hydatidiform mole (Schmitt et al., 2013).

Similarly, in a retrospective study carried out in Charing Cross Hospital Trophoblast Disease Centre including 9,586 patients with partial hydatidiform mole, three patients went on to develop post-molar gestational trophoblastic neoplasia. The study found for women with partial hydatidiform mole the risk of post-molar gestational trophoblastic neoplasia developing at the point of hCG normalisation was very low at 1 in 3195. This risk of pGTN developing was reduced three-fold after six months to 1 in 9584 (Coyle et al., 2018). Although these concordant data do not definitely exclude the possibility of GTN, they do suggest that the risk is too low to justify follow-up after hCG normalisation in patients with partial hydatidiform mole (Coyle et al., 2018, Schmitt et al., 2013).

Pending further research, it may be reasonable to recommend stopping surveillance in PHM patients from the date of normalisation of hCG.

Based on suggestions from external reviewers and the guideline development group, it was agreed that patients with PHM should have their serum hCG monitored weekly until normalisation and one further confirmatory hCG measurement is performed four weeks later. If that confirmatory hCG is normal then follow-up is complete (Figure 2).

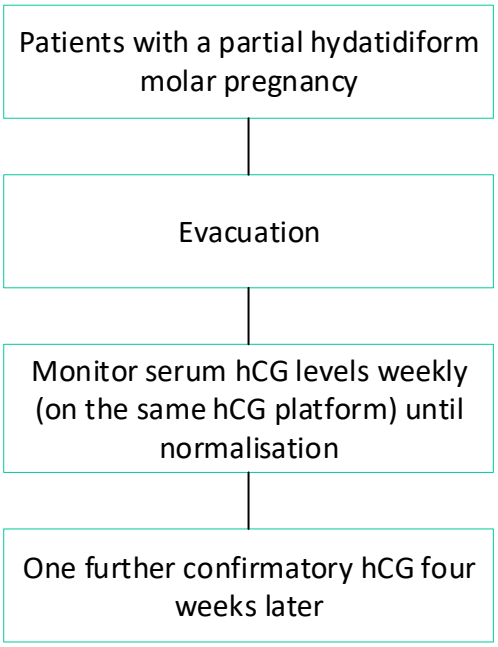


Figure 2 The current protocol for monitoring hCG levels in women with partial hydatidiform mole

Benefit and Harm

The guideline development group identified that patients with a partial hydatidiform molar pregnancy would benefit from not having to continue monitoring following confirmation of normalisation of hCG as this means fewer blood tests and the potential to try for a future pregnancy sooner.

However, patients with a complete hydatidiform molar pregnancy are at a higher risk of recurrence following normalisation of hCG. These patients may need chemotherapy and should be monitored.

Preferences and values

The guideline development group, which included patient representatives, agreed it is important for the patient's peace of mind to know that they are being followed up appropriately. The guideline development group agreed that the value of autonomy around starting a family outweighs the benefit of follow up for a rare recurrence. Patients with CHM will be reassured to continue follow-up.

Resources and other considerations

No cost-effectiveness literature was identified to address this clinical question.

The following resources and other considerations were discussed in detail by the guideline development group:

Dissemination of this National Clinical Guideline

Dissemination of this National Clinical Guideline to relevant stakeholders is important to ensure patients are not over/under managed or monitored. This dissemination plan is detailed in section Appendix V: Implementation plan.

Centralisation of serum hCG testing

Centralisation of serum hCG testing is discussed in further detail in clinical question 2.2.7. A business case for centralisation of serum hCG testing has been developed and is available as an Annex to this document.

Recommendation 2.2.6.1:

For patients with complete hydatidiform mole, serum hCG is monitored weekly (on the same platform) until normalisation is achieved for three weeks.

- If this occurs within eight weeks post evacuation then monitor monthly for six months from the time of evacuation.
- If normalisation occurs greater than eight weeks post evacuation then monitoring continues monthly for six months post normalisation.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.2.6.2:

For patients with partial hydatidiform mole, serum hCG should be monitored weekly (on the same platform) until normalisation and one further confirmatory hCG measurement should be performed four weeks later. If that confirmatory hCG is normal then follow-up is complete.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Good Practice Point

For all women with a previous diagnosis of GTD, early fetal ultrasound is standard practice to ensure a normal intrauterine pregnancy and to rule out recurrence of a molar pregnancy.

Good Practice Point

If a normal intrauterine pregnancy is confirmed there are no extra investigations necessary during the pregnancy.

Good Practice Point

For all women with a previous diagnosis of GTD, any subsequent pregnancy should be followed with a serum hCG measurement at six and ten weeks postnatally regardless of the outcome of pregnancy.

Good Practice Point

Serum hCG should be monitored on an assay that is CE marked for use in oncology (please refer to clinical question 2.2.5 for more information).

Clinical question 2.2.7

In women with confirmed GTD should monitoring of hCG be centralised?

Quality of evidence

A number of international guidelines agree that hCG should be performed in the same laboratory and on the same platform to ensure consistency of results (Tidy et al., 2020, Bolze et al., 2015, ESMO - Seckl et al., 2013, Goff, 2019).

Benefit and Harm

The guideline development group identified the following benefits of centralising hCG testing and monitoring:

- A standardised approach to disease management that would provide clinical staff and patients with hCG results from a fully governanced GTD centre.
- It is of benefit to clinicians and all patients with GTD to offer more efficient hCG testing to improve patient management.
- It would enable investigation of low level hCG persistence by scientists with expertise in GTD management.
- Troubleshooting hCG results that do not fit with clinical assesment to exclude analytical error (eg. antibody interference, high dose hook effect) and to inform multidisciplinary team discussions.
- All results will be available from a single accrediated laboratory that will use assays that are CE marked for oncology.
- Equity of access for all patients and faster turnaround time of results.

The guideline development group identified the following disadvantage to centralising hCG testing and monitoring:

- Logistics of transporting samples to a centralised laboratory.

Preferences and values

The guideline development group which included patient representatives agreed that centralisation of hCG testing provides patients with more confidence and timely information providing reassurance. Measurement of hCG at a centralised laboratory would facilitate equity of access to the expertise in the National GTD Registry, Monitoring and Advisory Centre

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question.

The following resources and other considerations were identified by the guideline development group:

Capacity of the National GTD registry, monitoring and advisory centre

It is time and resource intensive on the specialist nursing staff in the GTD Centre to gather and follow-up patient's hCG results from laboratories across the country.

Centralisation of serum hCG testing

A business case for a National hCG Diagnostic Service for Gestational Trophoblastic Disease has been developed and is available as an Annex (link). It details cost and funding estimates for centralisation of serum hCG testing which has the potential to be cost saving for other laboratories. It would enable international comparison of GTD centres and clinical audit to assess the benefits of a centralised service to patients.

hCG tumour marker code

New proposed code for hCG tumour marker testing (TMHCG) to distinguish routine hCG pregnancy testing from oncology use, to facilitate referral testing and future service audits. Research to facilitate international comparison of GTD centres and clinical audit to assess the benefits of a centralised service to patients.

Recommendation 2.2.7.1:
hCG testing should be centralised in women with confirmed GTD who have been registered with the National GTD Registry, Monitoring and Advisory Centre.

Quality of Evidence: Very Low **Grade of recommendation:** Strong

Good Practice Point
The registration of women with suspected GTD with the National GTD Registry, Monitoring and Advisory Centre represents a minimum standard of care.

2.3 Staging

The following are responsible for the implementation of the recommendations regarding staging: While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.3.1

For women with Gestational Trophoblastic Neoplasia (GTN), what investigations should be done to accurately stage GTN?

Quality of evidence

GTN includes: invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT).

Staging investigations and treatment stratification after a molar pregnancy

The evidence to inform this clinical question comes from two retrospective studies (Darby et al., 2009, Price et al., 2015) and international guidelines (ESMO - Seckl et al., 2013, Lok et al., 2020).

Most patients developing persistent disease post-hydatidiform mole (HM) are detected early via hCG monitoring and so extensive investigation is rarely required. Information to determine therapy can be obtained from the clinical history, examination, measurement of serum hCG and a Doppler pelvic ultrasound to confirm the absence of a pregnancy, to measure the uterine size/volume, spread of disease within the pelvis and its vascularity. (ESMO - Seckl et al., 2013)

Ultrasound is performed to rule out pregnancy in all patients. Once pregnancy is ruled out the guideline development group recommend a computed tomography (CT) thorax, abdomen and pelvis scan should be performed in order to accurately stage GTN. If lung metastases are present on a CT scan of the thorax a contrast enhanced MRI of the brain should be performed (Figure 3).

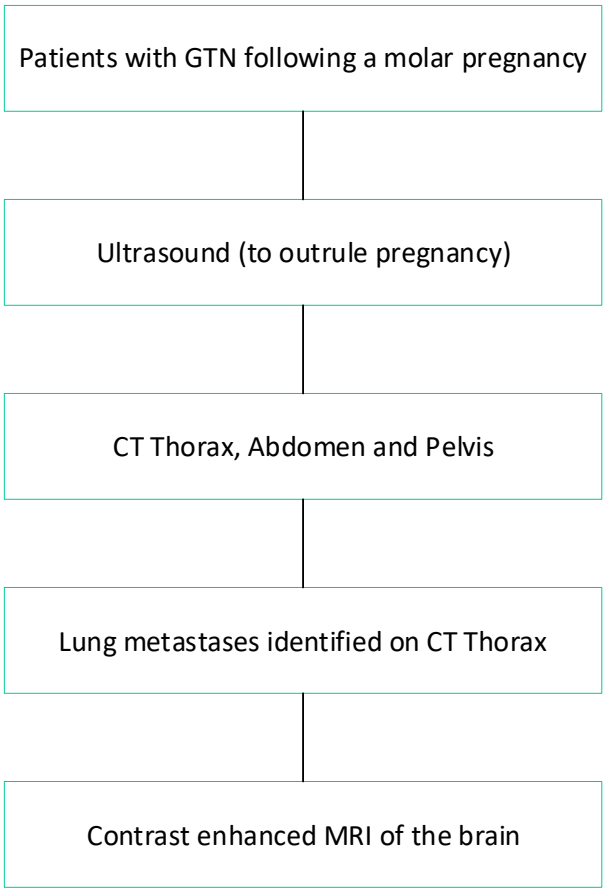


Figure 3 Radiological investigations for patients with GTN following a molar pregnancy detected by hCG surveillance

Staging investigations for choriocarcinoma (CC), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT)

Women who present with an elevated hCG and suspected GTN (CC, PSTT and ETT) following a prior pregnancy require much more extensive staging investigations, which include a contrast enhanced CT of the thorax and abdomen, MRI of the brain and pelvis, and may benefit from a lumbar puncture to assess the cerebrospinal fluid to serum hCG ratio. The latter if more than 1:60 suggests occult central nervous system disease (Seckl et al., 2010). In addition, where there is doubt over the clinical diagnosis, tissue should be obtained and genetic analysis undertaken to confirm the gestational origin of the tumour through the presence of paternal genes. (ESMO - Seckl et al., 2013)

Biopsy proof of GTN is not required unless PSTT/ETT is considered.

Benefit and Harm

The guideline development group identified that the patient would benefit from staging and appropriate treatment. It was agreed that CT TAP as a baseline can be useful as a comparator and that the benefit of the information gained through carrying out a CT TAP outweighs the potential harm of additional radiation dose.

Preferences and values

The guideline development group which included patient representatives agreed that CT TAP gives the patients peace of mind and provide reassurance that they have been accurately staged and will receive appropriate treatment. Patients may prefer to have a CT TAP as it provides reassurance.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this question.

The guideline development group identified the following barriers to implementing the recommendations.

Timely access to diagnostics

The guideline development group identified the importance of access to timely diagnostics in patients with GTN as an issue. It was agreed to include the timeframe of one week from diagnosis to staging investigation in the clinical recommendation to ensure patients have access to diagnostics in a timely manner.

Recommendation 2.3.1.1:

Women with a diagnosis of GTN should have serum hCG monitoring, ultrasound and a CT scan of thorax, abdomen & pelvis performed within one week of diagnosis.

Quality of Evidence: Low **Grade of recommendation: Strong**

Recommendation 2.3.1.2:

If clinically significant lung metastases are present on a CT scan of the thorax a contrast enhanced MRI of the brain should be performed.

Quality of Evidence: Low **Grade of recommendation: Strong**

Good Practice Point

Investigation and management decisions should be performed by experienced professionals in the management of GTD.

Practical considerations around patient care

- Patients should be counselled and reassured of the high cure rate of this patient cohort.

✓ **Retained 2015**

Clinical question 2.3.2

For women with GTN, what risk scoring system should be used to stage GTN?

Quality of evidence

The International Federation of Gynecology and Obstetrics (FIGO) reports data on GTN using anatomic staging systems (Table 1) and prognostic scoring (Table 2) (FIGO, 2009).

Since 2002, all physicians treating GTN should use this system to enable the comparison of data. The prognostic score predicts the potential for developing resistance to single-drug chemotherapy with methotrexate or actinomycin D. A score of 0–6 and ≥7 indicates a low- and high-risk of resistance, respectively. The latter has almost no chance of being cured with single drug therapy and requires multi-agent treatment. The anatomical staging not only helps with determining therapy, but provides additional information to help clinicians who compare results between centres.

Table 1 FIGO Anatomical Staging as adapted by FIGO (2009)

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

Table 2 Modified WHO prognostic scoring system as adapted by FIGO (2009)

	Scores			
Prognostic factor	**0**	**1**	**2**	**4**
Age	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	
Interval months from index pregnancy	<4	4-6	7-12	>12
Pre-treatment serum hCG IU/L	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
Largest tumour size (including uterus)	<3 cm	3-4 cm	≥5cm	-
Site of metastases	Lung	Spleen Kidney	Gastrointestinal	Liver Brain
Number of metastases	-	1-4	5-8	>8
Prior failed chemotherapy	-	-	1 drug	2 or more drugs

Staging notation uses a Roman numeral followed by an Arabic numeral that indicate FIGO anatomic staging and the WHO modified score, respectively. Placental site trophoblastic tumour (PSTT) and Epithelioid trophoblastic tumour (ETT) are classified separately (Biscaro et al., 2015). The total score for a patient is obtained by adding the individual scores for each prognostic factor: Low-risk 0-6; high-risk ≥7. Decision making based on the risk score (i.e. choosing and administering chemotherapy) should be made by experienced professionals in this area.

PSTT and ETT should not be scored and instead require separate classification in consultation with international experts (Biscaro et al., 2015, ESMO - Seckl et al., 2013). Consideration should be given to discussing borderline patients with international experts. Some reports suggest that patients with prognostic scores of 5 or 6 may be at an increased risk of resistance to single-agent chemotherapy. In a study by Taylor et al. (2013), over half the patients defined by FIGO/WHO score as low-risk (score 0–6) had a complete response to first-line treatment with methotrexate/folinic acid (60%). However, patients with a total FIGO/WHO score of 6 or hCG level of >100,000 IU/L had significantly higher rates of resistance. Only 19% of patients with a FIGO/WHO low-risk score of 6 and 16% with an hCG level of >100,000 IU/L achieved a complete response to methotrexate/folinic acid. Research is ongoing to try to better define which "low-risk" patients may particularly benefit from primary combination chemotherapy (Sita-Lumsden et al., 2012, Taylor et al., 2013).

Recommendation 2.3.2.1:
Women with GTN (invasive mole, choriocarcinoma) should be assigned a FIGO score to direct management decisions of chemotherapy regimens.

Grade of recommendation: Grade B

Good Practice Point
Placental site trophoblastic tumour and epithelioid trophoblastic tumour should not be scored using the FIGO system. They require separate classification in consultation with international experts.

2.4 Treatment

The following are responsible for the implementation of the recommendations regarding treatment:
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.4.1

For women with GTN, what are the clinical indicators to diagnose GTN warranting chemotherapy?

Quality of evidence

Three retrospective cohort studies (Agarwal et al., 2012, Braga et al., 2018, Braga et al., 2016) and an international guideline (ESMO - Seckl et al., 2013) addressed this clinical question.

The United Kingdom indications for commencing chemotherapy are listed below and are broadly similar to those of the International Federation of Gynecology and Obstetrics (FIGO) (Kohorn, 2002). The commonest is a plateaued or rising human chorionic gonadotropin (hCG), but others include a tissue diagnosis of choriocarcinoma (CC) and spread to other organs. The United Kingdom (UK) experience indicates that the disease is also unlikely to spontaneously remit if the hCG is >20,000 IU/L one month after hydatidiform mole (HM) evacuation (also associated with an increased risk of uterine perforation) or there are lung or vaginal metastasis of >2 cm (smaller lesions may spontaneously regress) (Seckl et al., 2010). In addition, in the UK, chemotherapy is started to help stop heavy bleeding that requires transfusion even if the hCG is falling. (ESMO - Seckl et al., 2013)

Recent data have suggested that surveillance is adequate for some women who continue to have a falling hCG six months after evacuation (Agarwal et al., 2014, Braga et al., 2016). However these decisions must be made on an individual patient basis following consultation with clinicians experienced in GTN management.

Indications for chemotherapy following the diagnosis of GTN:

- Plateaued or rising hCG after evacuation[1],
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage,
- Histological evidence of choriocarcinoma (except in exceptional circumstances),
- Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities larger than 2 cm on chest radiograph.

The following patients should be discussed on an individual basis with experienced professionals:

- Women with a serum hCG of 20,000 IU/L or more, four weeks or more after evacuation, because of the risk of uterine perforation (Braga et al., 2018)
- Women with a raised hCG six months after evacuation, even when hCG is still decreasing as a significant number of patients will achieve spontaneous remission (Braga et al., 2016).

Benefit and Harm

The guideline development group identified that patients would benefit from decisions on their treatment being made by professionals experienced in this disease. This includes the continued follow-up of patients with a decreasing hCG for six months after evacuation which may allow for avoidance of chemotherapy.

Continuous follow-up of hCG may be difficult for patients as they have to continue attending their hospital/GP for regular blood tests which may have a financial implication for patients.

Preferences and values

The guideline development group which included patient representatives identified that in women who do need chemotherapy there is certainty that the decision is being made with clinicians experienced in this disease.

In women whose hCG continues to fall after six months continous follow-up may be difficult (emotionally,

[1] * Plateaued or rising is defined as four or more equivalent values of hCG over at least three weeks (days 1, 7, 14, and 21) and three consecutive rises in hCG of 10% or greater over at least two weeks (days 1, 7, and 14), respectively.

logistically and financially) but avoiding chemotherapy and its associated complications is of greater value to the patient.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this question.

Serum hCG testing

hCG follow-up may have a financial implication for patients as a small number of women attend their GP for follow-up blood tests incurring personal cost. Patients may also attend an early pregnancy unit for blood tests, which patients find very distressing. The guideline development group agreed that it would be useful for the GP to receive a booklet along with a letter from the GTD centre regarding their patients care and that patients attending a regular phlebotomy unit should be facilitated where possible.

Recommendation 2.4.1.1:

Indications for chemotherapy following diagnosis of GTN:

- Plateaued or rising hCG after evacuation,
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage,
- Histological evidence of choriocarcinoma, except in exceptional circumstances,
- Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities of >2cm on chest x-ray.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.4.1.2:

Women who have a raised hCG six months after evacuation with a falling hCG should have their treatment plan discussed with the National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre.

Quality of Evidence: Low **Grade of recommendation: Strong**

Recommendation 2.4.1.3:

Women with serum hCG of ≥20,000 IU/L more than four weeks after evacuation should have their treatment plan discussed with the National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre.

Quality of Evidence: Low **Grade of recommendation: Strong**

Good Practice Point

For women with histological evidence of choriocarcinoma primary surgery may be considered.

Good Practice Point

The treating physician should ensure that the patient is registered with the National GTD Registry, Monitoring and Advisory Centre.

Clinical question 2.4.2

For patients with low-risk (FIGO 0-6) GTN, what is the optimal first-line chemotherapy regimen?

Quality of evidence

Three retrospective studies (Lybol et al., 2012, Hasanzadeh et al., 2014, Taylor et al., 2013) an international guideline (ESMO - Seckl et al., 2013) and experience from an expert centre (Charing Cross Hospital, 2019) addressed this clinical question.

Low-risk disease is characterised by any one of the following:

- FIGO stage I GTN – This is characterised as a persistently elevated human chorionic gonadotropin (hCG) level and/or tumour confined to the uterus
- Stage II or III GTN with a WHO risk score 0-6.

For nearly all low-risk GTN patients, single-agent chemotherapy with either methotrexate or actinomycin D is the standard treatment. A variety of regimens have been developed. The variability in regimens reflects differences in dose, frequency and route of administration as well as criteria used to select patients for therapy (Berkowitz and Goldstein, 2009). Some investigators have argued that more intense therapies given daily over 5–8 days every two weeks are superior to treatments given once every two weeks (Kohorn, 2002). Others have suggested that actinomycin D is more likely to induce remission than methotrexate. The few randomised studies to address some of these issues (Osborne et al., 2011) have been underpowered and compared regimens that are not frequently used internationally (Alazzam et al., 2011). (ESMO - Seckl et al., 2013)

Importantly, in patients with persistent disease after first-line therapy, usually because of resistance, can be easily treated with second and occasionally third-line chemotherapy so that the overall survival (OS) is ~100% (Lurain et al., 2012, McNeish et al., 2002, Sita-Lumsden et al., 2012). As survival is so high, it seems sensible to start with the least toxic therapy first to minimise the exposure of patients to more harmful treatments. (ESMO - Seckl et al., 2013)

A recent retrospective cohort study (Cortés-Charry et al., 2021) found that in 609 GTN patients who commenced treatment with MTX/FA 57% achieving a complete response. Resistance developed in 25.1% at an hCG 1000 IU/l and switching to Actinomycin D achieved remission in 92.8% without any major toxicity with the remaining 7.2% remitting on EMA/CO.

The methotrexate with folinic acid rescue regimen developed at Charing Cross Hospital is effective, well tolerated and unlike actinomycin D, does not induce hair loss, so methotrexate with folinic acid has been widely adopted (McNeish et al., 2002). (ESMO - Seckl et al., 2013)

Non-randomised data suggest that reducing the consolidation therapy by just one cycle doubles the risk of relapse (Lybol et al., 2012). This provides justification for the current regimen of three consolidation cycles of methotrexate after hCG normalisation.

In a study by Hasanzadeh et al. (2014) the efficacy of weekly IM methotrexate regimen with dose escalation in low-risk GTN was 74.3%, which is the highest rate among present studies. Additionally, this study showed that the mentioned methotrexate regimen was less effective in patients with score 5 and 6, especially score 6. Therefore, more schedules should be performed to make changes in management, therapeutic protocols, and also classification of this group. Similarly in a retrospective study carried out by Taylor et al. (2013) 173/289 patients (60%) treated with methotrexate/folinic acid achieved a complete biochemical response, while 116 patients (40%) developed resistance. A more recent retrospective cohort study (Braga et al., 2021) of 431 patients with a FIGO score of 5 or 6 found that 60% of patients had remission with one or two sequential

single-agent therapies.

Central nervous system (CNS) prophylaxis
Charing Cross Hospital's policy is to give prophylaxis to low-risk patients with lung metastases. Treatment is intrathecal methotrexate (12.5mg) followed by oral folinic acid (15mg at 24 hrs) on three occasions during the first three methotrexate courses.

Benefit and Harm
The guideline development group identified that survival rates are high with both methotrextate and actinomycin D. Treatment of patients with methotrexate is less toxic than actinomycin D and does not result in hair loss. Patients receiving actinomycin D may require admission as an in-patient.

Preferences and values
While disease progression will occur in 40% of patients (Taylor et al., 2013), the guideline development group which included patient representatives agree that it is preferred to start with the less toxic therapy. Meaning, reduced side effects, avoidance of hair loss and complications whilst undergoing treatment.

Resources and other considerations
One cost-effectiveness analysis was identified to address this question (Miller et al., 2017).

Miller et al. (2017) constructed a cost-effectiveness decision model from the third party payer perspective comparing weekly intramuscular methotrexate (30 mg/m^2) with biweekly pulsed intravenous dactinomycin (Act-D, 1.25 mg/m^2 IV) as single-agent chemotherapy for low-risk gestational trophoblastic neoplasia (GTN).

The analysis included clinical data from the Gynecologic Oncology Group (GOG) 0174 randomised trial (Osborne et al., 2011) of 240 women with low risk GTN. Costs for each arm were in 2014 US dollars and were obtained through publicly available databases. One-way sensitivity analyses were performed by varying treatment costs, rates of cure, and QOL-related utility scores.

The study found that Act-D ($18,505) was more expensive compared to weekly methotrexate ($8,950) with an ICER of $56,215 per first-line treatment success compared to weekly methotrexate. Small decreases in QOL dramatically increased the ICER during sensitivity analysis. Models with multi-day methotrexate regimens were also more cost-effective than Act-D. If effectiveness was redefined as avoidance of multi-agent chemotherapy, weekly MTX was more effective. The generalisability of this study to the Irish context is limited as the methotrexate doses in this study are not comparable to those used in Ireland. The GOC 0174 trial was conducted in North America where the most commonly used methotrexate regimen is 30mg/m^2, in Ireland the most commonly used methotrexate regimen is 50 mg/m^2.

The guideline development group identified the following potential barriers to implementation of the recommendations:

Patients diagnosed with GTN should have access to a designated point of contact in the treatment centre who should also be in contact with the National GTD Registry, Monitoring and Advisory Centre.

Recommendation 2.4.2.1:
Patients with a FIGO score of 0-6 can be treated with either single-agent methotrexate with or without folinic acid, or actinomycin D. Taking into account the treatment cycles, potential complications and quality of life the guideline development group agreed that the IM methotrexate 8 day regimen is the preferred first-line chemotherapy.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.4.2.2:
Chemotherapy for low-risk disease should be continued for three cycles of consolidation treatment at the standard two weekly cycle after hCG normalisation.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Good Practice Point
In patients with low risk GTN serum hCG/blood should be measured prior to each chemotherapy cycle or more frequently if required. Normalisation of hCG values should be assay specific.

Practical considerations around patient care

- Patients diagnosed with GTN should have access to counselling and support from the nurses in the National GTD Registry, Monitoring and Advisory Centre.
- Patients diagnosed with GTN should have access to a liasion nurse or designated key contact in the patient's treatment centre who should also be in contact with the National GTD Registry, Monitoring and Advisory Centre.

Clinical question 2.4.3

For women with high-risk (FIGO ≥7) GTN, what is the optimal first-line chemotherapy regimen?

Quality of evidence

High-risk gestational trophoblastic neoplasia (GTN) is characterised by any one of the following:

- Stage IV disease
- Stage II and III with risk score ≥7.

A Cochrane meta-analysis (Deng et al., 2013), a retrospective study (Alifrangis et al., 2013) and experience from an international centre Charing Cross (2019) addresed this clinical question.

EMA/CO (etoposide, methotrexate, actinomycin D plus cyclophosphamide and vincristine) is currently the most widely used first-line combination chemotherapy for high-risk GTN, although this regimen has not been rigorously compared to other combinations such as MAC (methotrexate, actinomycin D, cyclophosphamide or chlorambucil) or FAV (5-FU, actinomycin D, and vincristine) in randomised controlled trials. Other regimens may be associated with less acute toxicity than EMA/CO; however, proper evaluation of these combinations in high quality RCTs that include long-term surveillance for secondary cancers is required. Given the low incidence of GTN, RCTs in this field are difficult to conduct, hence multi-centre collaboration is necessary. CHAMOCA (cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan and vincristine) is not recommended for GTN treatment as it is more toxic and not more effective than MAC. (Deng et al., 2013)

A recent retrospective study by Alifrangis et al. (2013) demonstrated that during the period 1995 to 2010, overall survival for all patients with GTN treated with EMA/CO chemotherapy significantly increased from 86.2% before 1995 to 97.9%. EP induction chemotherapy was given to 23.1% of high-risk patients (33 of 140 patients) with a large disease burden, and the early death rate was only 0.7% (n = 1; 95% CI, 0.1% to 3.7%) compared with 7.2% (n = 11 of 151 patients; 95% CI, 4.1% to 12.6%) in the pre-1995 cohort. However, high-risk patients receiving EP, compared with patients not receiving EP, did have a higher but not statistically significant relapse rate (9% v 6%, respectively; P = .44) and death rate (12% v 4%, respectively; P = .088).

Central nervous system (CNS) prophylaxis

Charing Cross Hospital's policy is to give prophylaxis to all high-risk patients. Treatment is intrathecal methotrexate (12.5mg) followed by oral folinic acid (15mg at 24 hrs) on three occasions during the first three methotrexate courses, which usually coincides with the CO treatment.

Benefit and Harm

The guideline development group identified that commencing treatment with EMA/CO provides a greater opportunity for curative treatment and is consistent with Charing Cross Hospital and other European GTD centres, this treatment regimen does not have a significant impact on fertility.

Following the use of EMA/CO there can be treatment-related toxicity including inducing menopause on average three years early.

Preferences and values

The guideline development group which included patient representatives agreed that patients would choose the multi-agent chemotherapy due to the greater opportunity for curative treatment.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question

Recommendation 2.4.3.1:
Patients with a FIGO score of ≥7 should receive multi-agent chemotherapy and most centres now use EMA/CO, as it is highly effective.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Recommendation 2.4.3.2:
Early deaths in ultra-high-risk GTN (FIGO score >12) can be reduced by induction therapy with low dose etoposide and cisplatin. Such patients may also benefit from substitution of EMA/CO with EMA/EP.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Good Practice Point
For women with high-risk GTN, decisions should be made on an individual patient basis following discussion with clinicians experienced in high-risk GTN management at a GTD Centre.

Good Practice Point
Registration of patients at the National GTD Registry, Monitoring and Advisory Centre is a minimum standard of care.

Practical considerations around patient care

- Patients should be informed that their treatment will require in-patient care.
- Patients with high-risk GTN (FIGO score of ≥7) should have access to a liaison nurse or designated key contact locally who is in contact with the National GTD Registry, Monitoring and Advisory Centre.
- Patients diagnosed with GTN should have access to a liaison nurse or designated key contact in the patient's treatment centre who should also be in contact with the National GTD Registry, Monitoring and Advisory Centre.

✓ **Retained 2015**

Clinical question 2.4.4

For women with low-risk GTN undergoing chemotherapy (first-course), what is the recommended course of action for observing and managing bleeding?

Quality of evidence

The guideline development group recommends that the first one/two courses of chemotherapy should be administered as an inpatient at a centre with medical oncology, gynaecological services and interventional radiology. Subsequent courses in uncomplicated patients are administered at a medical oncology day ward facility.

If hCG levels are very high, the uterine mass large or there is evidence of vaginal metastases, patients may be kept in for two complete courses or longer due to the risk of haemorrhage (Seckl and Savage, 2012).

Per vaginal or intraperitoneal bleeding can occur. Moderate bleeding usually responds to bed rest and chemotherapy. Torrential bleeding may require treatment with a vaginal pack, blood products, anti-fibrinolytics, emergency embolisation and very rarely with hysterectomy.

In Charing Cross experience, less than 1.5% of GTN patients have required one of these interventions over the past 25 years (Charing Cross Hospital, 2019).

Recommendation 2.4.4.1:

For women with low-risk GTN undergoing first-line chemotherapy, the first ± second courses of chemotherapy should be administered as an in-patient at a centre with medical oncology, gynaecological services and interventional radiology.

Grade of recommendation: Grade C

Clinical question 2.4.5

For women with GTN, what are the appropriate investigations to monitor response to chemotherapy and follow-up?

Quality of evidence

Monitoring response to chemotherapy – Low-Risk

Patients should have hCG levels measured prior to their next chemotherapy cycle (Lok et al., 2020). Treatment is continued until hCG is normal and then usually for three further courses to eliminate any residual tumour cells and to minimise the chances of relapse. Non-randomised data suggest that reducing the consolidation therapy by just one cycle doubles the risk of relapse (ESMO - Seckl et al., 2013).

Monitoring response to chemotherapy – High-Risk

Patients should have hCG levels measured prior to their next chemotherapy cycle (Lok et al., 2020). Therapy is continued for 6 weeks of normal hCG values or 8 weeks if poor prognostic features such as liver or brain metastases are present. Patients are then re-imaged to document the post-treatment appearance for future comparison. Removal of residual masses is unnecessary as it does not reduce the risk of recurrence which is less than 3% (Seckl et al., 2010). (ESMO - Seckl et al., 2013)

Follow-up of patients post chemotherapy

After remission is achieved, serum hCG should be measured fortnightly for six months after consolidation therapy then monthly for a further six months and every two months for two years (Balachandran et al., 2019).

Follow-up for at least 5 years may be considered for those at highest risk.

Benefit and Harm

The guideline development group agreed that patients would benefit from having their hCG monitored during and following treatment as it allows for timely treatment management. Continuous follow-up of hCG may be difficult for patients as they have to continue attending their hospital/GP for regular blood tests and there may be a delay in trying for a subsequent pregnancy.

Preferences and values

The guideline development group which included patient representatives agreed that the value of autonomy around starting a family outweighs the benefit of follow-up for a rare recurrence.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question.

The guideline development group identified the following barriers to implementing the recommendations:

Centralisation of hCG testing – the group identified that patients may benefit from urine assays as this would allow for a longer follow-up without causing patients to undergo blood tests. The issue of centralisation of hCG testing is covered in clinical question 2.4.5

The guideline development group agreed that the recommendations were suitable for audit.

Recommendation 2.4.5.1:
Monitoring during treatment in patients with low-risk GTN:
Patient should have hCG levels measured prior to their next chemotherapy cycle. Treatment is continued until hCG is normal and for three further consolidation cycles.

Quality of Evidence: Low **Grade of recommendation: Strong**

Recommendation 2.4.5.2:
Monitoring during treatment in patients with high-risk GTN:
Patient should have hCG levels measured prior to their next chemotherapy cycle. Patients with high-risk disease should have consolidation therapy for three cycles after hCG normalisation extended to four cycles for patients with poor prognostic features such as liver metastases with or without brain metastases.

Quality of Evidence: Low **Grade of recommendation: Strong**

Recommendation 2.4.5.3:
Follow-up post treatment:
After remission is achieved, serum hCG should be measured fortnightly for six months then monthly for a further six months and every two months for two years.

Quality of Evidence: Moderate **Grade of recommendation: Strong**

Practical considerations around patient care

- Patients should have access to a nurse or designated key contact with experience treating GTN that can provide advice, written information and support to patients before commencing treatment.
- Patients should be provided with clear written information in patient-friendly language that they can share with family.

✓ **Retained 2015**

Clinical question 2.4.6

For women with gestational trophoblastic neoplasia what are the indicators to determine switching treatments from first-line chemotherapy?

Quality of evidence

Chemotherapy should continue until hCG returns to normal, and at least three more chemotherapy cycles should be administered after the first normal hCG result (Lybol et al., 2012). The drug in use should be replaced by another when there is an inadequate response i.e. a rise in hCG values over two successive measurements a week apart or a plateau in three successive weekly measurements a week apart or when toxicity (such as mucositis, pleuritic chest pain or abdominal pain) precludes the use of appropriate doses or treatment frequency.

About 5% of patients with low-risk GTN without metastases and 10-15% of those that have metastases develop resistance to first-line chemotherapy (Lurain and Nejad, 2005). (Biscaro et al., 2015)

Resistance to chemotherapy and recurrent disease are more frequent in patients with high risk GTN (Berkowitz and Goldstein, 2013). About 20-30% of high-risk patients have an incomplete response to first-line chemotherapy or recurrence after remission and eventually need salvage chemotherapy. (Biscaro et al., 2015)

Recommendation 2.4.6.1:

For patients with low-risk GTN the clinical indicators for a change in treatment from first-line chemotherapy include: treatment related toxicity, a rise in hCG values over two successive measurements a week apart or a plateau in three successive weekly measurements a week apart.

Grade of recommendation: Grade C

Good Practice Point

Consideration could be given to re-staging patients prior to the initiation of a new regimen (particularly high-risk patients).

Clinical question 2.4.7

For women with low-risk gestational trophoblastic neoplasia who have not responded or have relapsed from single agent treatment (methotrexate or actinomycin D) or have relapsed following normalisation of hCG after completion of single agent treatment, what is the next line treatment?

Quality of evidence

First line methotrexate

The next line of treatment is determined by the patient's current hCG levels, with those with hCG levels <1,000 IU/L receiving single-agent actinomycin D and those with hCG levels of >1,000 IU/L commencing on EMA–CO (Lok et al., 2020).

For women with low-risk GTN if sequential single-agent therapy fails, multi-agent chemotherapy must be used to achieve a cure; this is necessary in 6% to 15% of cases (Covens et al., 2006, Goldstein and Berkowitz, 2012). The multi-agent therapy used most frequently at Charing Cross (one of two treatment centres in the UK) is EMA/CO. The New England Trophoblastic Disease Centre (NETDC, USA) prefers to use MAC before EMA/CO owing to concerns that etoposide may be associated with an increased risk of secondary tumours (Goldstein and Berkowitz, 2012). (Alazzam et al., 2016)

A recent retrospective cohort study (Cortés-Charry et al., 2021) found that in 609 GTN patients who commenced treatment with MTX/FA 57% achieving a complete response. Resistance developed in 25.1% at an hCG 1000 IU/l and switching to ActD achieved remission in 92.8% without any major toxicity with the remaining 7.2% remitting on EMA/CO.

In Ireland the guideline development group recommends the use of EMA/CO as first-line combination therapy. All patients should be registered at the National GTD Registry, Monitoring and Advisory Centre. Patients should be treated under the care of a medical oncologist with experience in the treatment of GTN.

A retrospective study demonstrated an overall survival rate of 99.6%, in 250 low risk patients who received second-line EMA/CO after relapse or resistance to single-agent chemotherapy. Four patients (1.5%) developed resistance and/or experienced relapse after EMA/CO. These patients were all cured with further salvage regimens (Alifrangis et al., 2013).

Once normalistion of hCG has occurred on EMA/CO, treatment with etoposide can be discontinued from the regimen to reduce the risk of secondary malignancies. (Charing Cross Hospital, 2019)

Central nervous system (CNS) prophylaxis

Charing Cross Hospital's policy is to give prophylaxis to all high-risk patients and to the low-risk patients with lung metastases. Treatment is intrathecal methotrexate (12.5mg) followed by oral folinic acid (15mg at 24 hrs) on three occasions during the first three methotrexate courses. For the high-risk patients it usually coincides with the CO treatment.

Benefit and Harm

The guideline development group agreed that the patients who have not responded to methotrexate with a hCG <1,000 IU/L would benefit from treatment with actinomycin D as they could avoid treatment with multi-agent therapy including etoposide, as etoposide can increase the risk of secondary malignancies.

Patients with low-risk GTN who have not responded to methotrexate with a hCG >1,000 IU/L would benefit from treatment with EMA/CO as it reduces the risk of CNS involvement.

Preferences and values

The guideline development group which included patient representatives agreed that the use of a less toxic

treatment initially reserves the more toxic treatment for the minority of people who may need it. This will avoid unnecessary treatment-related toxicities for patients.

Resources and other considerations

No relevant cost-effectiveness studies were identified to address this clinical question.

The Guideline development group identified the following barriers and enablers to implementing the recommendation:

Recommendation 2.4.7.1:
For women with low-risk GTN who have not responded to methotrexate with a hCG <1,000 IU/L the next line of treatment is actinomycin D.

Quality of Evidence: Low **Grade of recommendation: Strong**

Recommendation 2.4.7.2:
For women with low-risk GTN who have not responded to methotrexate with a hCG >1,000 IU/L the next line of treatment is EMA/CO.

Quality of Evidence: Low **Grade of recommendation: Strong**

Recommendation 2.4.7.3:
For women with low-risk GTN who have not responded or have relapsed from sequential single-agent treatment the next line of treatment is combination chemotherapy with EMA/CO.

Quality of Evidence: Low **Grade of recommendation: Strong**

Good Practice Point
Once normalistion of hCG has occurred on EMA/CO treatment etoposide can be discontinued from the regimen to reduce the risk of secondary malignancies.

Clinical question 2.4.8

For women with high-risk GTN who have not responded to first-line treatment, what is second-line treatment?

Quality of evidence

In women with high-risk GTN who have not responded to first-line treatment, consideration should be given to discussing each individual case with an international expert due to the rarity of this condition.

Currently, the most commonly used salvage regimen in North America and the UK for the treatment of resistant or recurrent high-risk GTN is EMA/EP (May et al., 2011). A Cochrane review conducted by Alazzam et al. (2016) stated that approximately 90% of high-risk patients treated initially with EMA/CO, followed by salvage therapy with a platinum-etoposide combination if required, will survive (Lurain, 2010)(Lurain et al., 2010). In three series of EMA/EP salvage treatment following EMA/CO treatment failure, cure rates of 75% (nine out of 12 women; (Newlands et al., 2000)) 66.6% (12 out of 18 women; (Mao et al., 2007) and 84.9% (11 out of 13 women; (Lu et al., 2008)) were reported; however, EMA/EP was associated with significant myelosuppression and hepatotoxicity, leading to treatment delays and dose reductions. Myelosuppression may be minimised by administering granulocyte-colony stimulating factor (G-CSF) (El-Helw et al., 2005, Lurain and Nejad, 2005, Seckl et al., 2010).

An alternative to EMA/EP is TE/TP (paclitaxel/cisplatin and paclitaxel/etoposide). The taxane containing regimen was found to be associated with comparable cure rates to EMA/EP (70% of 10 patients who had not been exposed to previous EP treatment were cured) but with relatively reduced toxicity and no dose delays or reductions (Alazzam et al., 2016).

Central nervous system (CNS) prophylaxis

Charing Cross Hospital's policy is to give prophylaxis to all high-risk patients and to the low-risk patients with lung metastases. Treatment is intrathecal methotrexate (12.5mg) followed by oral folinic acid (15mg at 24 hrs) on three occasions during the first three methotrexate courses. For the high-risk patients it usually coincides with the CO treatment.

Benefit and Harm

The second line treatment for high risk patients is associated with toxicity including myelosuppression and hepatotoxicity. However, salvage treatment has a 90% cure rate, therefore the benefit of this second-line treatment outweighs the harm and toxicities associated with it.

Preferences and values

The guideline development group which included patient representatives agreed that patients would choose the second line chemotherapy due to the greater opportunity for curative treatment.

Resources and other considerations

No relevant cost-effectiveness literature was identified to address this clinical question.

Recommendation 2.4.8.1:
For women with high-risk GTN who have not responded to first-line treatment, second-line treatment is EMA/EP or TE/TP.

Quality of Evidence: Low **Grade of recommendation: Strong**

Recommendation 2.4.8.2:
In women with high-risk GTN who have not responded to first-line treatment, discussions of each individual case at a GTD MDM should be considered.

Quality of Evidence: Very Low	**Grade of recommendation: Strong**

Good Practice Point
All women with GTN should be registered at the National GTD Registry, Monitoring and Advisory Centre.

Good Practice Point
Given the rarity of this condition consideration should be given to discussing each individual case with international experts.

Clinical question 2.4.9

For women with GTN, who are acutely ill with liver, brain or lung metastasis at presentation, what is the optimum chemotherapy regimen?

Quality of evidence

Given the rarity of this condition consideration should be given to discussing each individual case with international experts.

Emergency treatment

Patients who are acutely unwell from liver or CNS disease and particularly those with large lung metastases who are at risk of respiratory failure should be admitted and emergency chemotherapy started as soon as possible as these patients can deteriorate rapidly (Charing Cross Hospital, 2019). This should start with low dose induction etoposide and cisplatin repeated weekly until the patient is well enough for standard dose chemotherapy.

Chemotherapy can be started with low dose induction EP (Table 3). This can be repeated weekly and then altered to EMA/CO or EMA/EP at a later point. Please refer to the NCCP Chemotherapy Regimen (NCCP regimen code: 00267) for more information.

Table 3 Two day Etoposide CISplatin (EP) Therapy

Day 1	Etoposide 100mg/m^2
	Cisplatin 20mg/m^2
Day 2	Etoposide 100mg/m^2
	Cisplatin 20mg/m^2

Hepatic metastases

Patients with hepatic metastases at presentation are usually diagnosed with ultra high risk disease (FIGO >12) and therefore should continue therapy using EMA/EP protocol following low dose induction EP (Charing Cross Hospital, 2019). Please refer to the NCCP Chemotherapy Regimen (NCCP regimen code: 00264) for more information.

Cerebral metastases

The Charing Cross Hospital's treatment for this is the high dose EMA (CNS)/CO, using an increased methotrexate dose (1gm/m^2) combined with longer folinic acid (FA) rescue. In CNS disease the EMA (CNS)/ CO chemotherapy is continued for eight weeks after the human chorionic gonadotropin (hCG) normalisation (Charing Cross Hospital, 2019).

Intrathecal methotrexate is also given as 12.5mg +15mg FA on the EMA week until serum hCG is normal at which point it is discontinued. Please refer to the NCCP Chemotherapy Regimen (NCCP regimen code: 00249) for more information.

In emergency situations with cerebral metastases, high-dose dexamethasone is given followed by two-day EP as above (Charing Cross Hospital, 2019).

Hepatic and synchronous cerebral metastases

In patients with liver and brain metastases the treatment used should be as follows (Table 4):

Table 4 Etoposide Methotrexate DACTINomycin/Etoposide CISplatin (EMA/EP) Therapy

Week 1	Day 1	Actinomycin-D 0.5mg IV (flat dose not m^2)
		Etoposide 100mg/m^2 IV
		Normal saline 1000ml + 20mMol KCl over 2hrs

		Methotrexate 1000mg/m2 in 1000ml normal saline over 24hrs IV
	Day 2	Folinic acid 30mg po 6 hourly x 12 doses
		Starting 32hrs after commencing methotrexate
Week 2	Day 8	Etoposide 150mg/m^2 IV
		Cisplatin 75mg/m^2 IV

This combines the EMA (CNS) dose with the EP treatment. It misses out the day two of the normal EMA protocol as it is too myelosuppressive when combined with EP to allow for this. We would use G-CSF (granulocyte – colony stimulating factor) for 3-5 days every week in between day 1 and 8 and day 8 and 1. Please refer to the NCCP Chemotherapy Regimen (NCCP regimen code: 00264) for more information.

Intrathecal methotrexate is also given 12.5mg + 15mg FA on the EP week until serum hCG is normal at which point it is discontinued (Charing Cross Hospital, 2019, Savage et al., 2015)

Respiratory failure
In patients with large volume pulmonary lung metastases oxygen support can be given but ventilation is contraindicated, due to the risk of traumatic haemorrhage from the tumour vasculature. Respiratory compromise can also result from tumour within the pulmonary vasculature. This can respond promptly to chemotherapy. Consideration can be given to anti-coagulation in these rare patients with tumour emboli (Charing Cross Hospital, 2019).

Interventional radiology
Consideration could be given to radiological embolization of lesions complicated by intractable bleeding.

Benefit and Harm
The urgent need for therapy outweighs potential side effects of treatment.

Preferences and values
The guideline development group which included patient representatives agreed that patients would choose the opportunity for curative treatment.

Resources and other considerations
No relevant cost-effectiveness literature was identified to address this clinical question.

Recommendation 2.4.9.1:
Emergency treatment
Patients who are acutely unwell from liver or CNS disease and particularly those with large lung metastases who are at risk of respiratory failure should be admitted and emergency chemotherapy commenced as soon as possible.

Quality of Evidence: Very Low **Grade of recommendation: Strong**

Recommendation 2.4.9.2:
Hepatic metastases
Patients with hepatic metastases at presentation should continue therapy using EMA/EP protocol.

Quality of Evidence: Very Low **Grade of recommendation: Strong**

Recommendation 2.4.9.3:
Cerebral metastases
Patients with cerebral metastases should be treated with EMA(CNS)/CO.

Quality of Evidence: Very Low **Grade of recommendation: Strong**

Recommendation 2.4.9.4:
Hepatic and synchronous cerebral metastases
Patients with liver and brain metastases should be treated with a combination of EMA (CNS) and EP.

Quality of Evidence: Very Low **Grade of recommendation: Strong**

Practical considerations around patient care

- Patients should be provided with reassurance that they are being managed in co-operation with the National GTD Registry, Monitoring and Advisory Centre.
- Patients should be counselled and reassured of the high cure rate of this patient cohort.

3.0 Development of a National Clinical Guideline

3.1 Epidemiology

In Ireland the data on incidence of GTD comes from the National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre which was established in May 2017. One of the objectives of the National GTD Centre is to register all women with GTD to ensure early detection of malignant change so that appropriate treatment can be instituted at the earliest possible time.

Table 5 provides a breakdown of the patients registered with the National GTD Centre in 2021 by mole classification. The most common mole classification registered with the National GTD Centre was partial hydatidiform mole, which made up approximately 62% of registrations. Twenty hospitals throughout the country registered patients with the National GTD Centre – more than a quarter of the patients (27%) registered were patients from Cork University Maternity Hospital. The low rate of registration from some large maternity hospitals is significant.

Table 5 Breakdown of patients registered with the National GTD Centre by mole classification in 2021

Mole Classification	Patients
Partial Hydatidiform Mole	85
Complete Hydatidiform Mole	46
Suspicion of Molar Pregnancy	5
Choriocarcinoma	1
PSN (Placental Site Nodule)	1
Total	**138**

A 2019 laboratory study estimated that 42% of women with suspected GTD/GTN were not registered with the National GTD Centre. Therefore the above figure on registration does not reflect the incidence and is likely to be an underestimation of the incidence of GTD in Ireland.

Recent research amongst women who have been registered with the National GTD Centre highlights the specific needs of women with molar pregnancy in terms of psychological support, bereavement counselling and peer support groups (Joyce et al., 2022).

3.2 Rationale for this National Clinical Guideline

In November 2015, the NCEC published the first iteration 'Diagnosis, staging and treatment of patients with gestational trophoblastic disease - National Clinical Guideline No. 13'.

The National Cancer Strategy 2017-2026 (Department of Health, 2017) recommends: The NCCP will develop further guidelines for cancer care in line with National Clinical Effectiveness Committee (NCEC) standards. The purpose of developing this guideline is to improve the quality of care delivered to patients.

3.3 Aim and objective

The overall objectives of the National Clinical Guideline No. 13 'Diagnosis, staging and treatment of patients with GTD' are:

- To improve the quality of clinical care,
- To prevent variation in practice,
- To address areas of clinical care with new and emerging evidence,
- Based on the best current research evidence in conjunction with clinical expertise and patient preferences and values,
- Developed using a clear evidence-based internationally used methodology.

3.4 Financial impact of GTD

The diagnosis, staging, and treatment of patients with GTD requires multidisciplinary care in an acute hospital setting. The majority of patients will require diagnostic tests (radiology, pathology) and depending on the treatment plan may require surgery and chemotherapy.

The guideline development group identified the issue of serum hCG testing for patients. hCG follow-up may have a financial implication for patients as a small number of women attend their GP for follow-up blood tests incurring personal cost. The guideline development group agreed that it would be useful for the GP to receive an information booklet along with a letter from the GTD centre regarding their patients care. Further details are included in Appendix IV: Economic assessment and Appendix V: Implementation plan.

The establishment of the National GTD Registry, Monitoring and Advisory Centre has aided in the identification of the volume of patients with GTD in the country, which has informed costs as outlined in Appendix IV: Economic assessment.

3.5 Guideline Scope

3.5.1 Target population

Patients covered by this guideline are: Women who have had a miscarriage, any woman who has had a molar pregnancy, any woman with unexplained elevated hCG, any woman presenting with metastatic disease of uncertain origin where the hCG is elevated, and any woman with atypical placental site nodules.

3.5.2 Target audience

This guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with GTD, such as gynaecologists, radiologists, pathologists, biochemists, surgeons, medical oncologists, GPs and nursing staff. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

This guideline is also relevant to those involved in clinical governance, in both primary and secondary care, to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients with GTD and their significant others. A list of medical abbreviations used throughout the guideline can be found in Appendix VIII: Glossary of terms and abbreviations.

3.6 Conflict of interest statement

A conflict of interest form was signed by all Guideline Development Group members and reviewers. The Guideline Development Group was managed by the Chair to promote the highest professional standard in the development of this guideline. Where a conflict arises a Guideline Development Group member absents themselves from discussion pertaining to their area of conflict.

3.7 Source of funding

The guideline was commissioned and funded by the NCCP however the guideline content was not influenced by the NCCP or any other funding body. This process was fully independent of lobbying powers. All recommendations were based on the best current research evidence integrated with clinical expertise and patient preferences and values.

3.8 Guideline methodology and literature review

The methodology for updating this national clinical guideline is outlined in the 'NCCP's methodology for updating National Clinical Guidelines' which is available upon request.

3.9 Consultation process

The draft guideline was signed off by the entire Guideline Development Group and the NCCP Guideline Steering Group before going to national stakeholder review. It was placed on the NCCP website and circulated to relevant organisations and individuals for comment between 26th of July 2021 and the 6th of September 2021. A full list of those invited to review this guideline is available in Appendix III: Details of consultation process.

Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. Stakeholders were required to submit feedback with supporting evidence on a form provided along with a completed conflict of interest form. A time-period of six weeks was allocated to submit comments.

3.10 External review

The draft guideline was also submitted for international expert review. The Guideline Development Group nominated Professor Michael Seckl, Charing Cross Hospital as International reviewer to provide feedback on the draft guideline. The reviewer was chosen by the Guideline Development Group based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the National Stakeholder Review. The guideline was circulated for comment between the 26th of July 2021 and the 6th of September 2021

All feedback received was reviewed by the guideline development group. Suggested amendments and supporting evidence were reviewed and consensus reached to accept or reject the amendments. All modifications were documented and the report is available upon request.

3.11 Implementation

The implementation plan (Appendix V: Implementation plan) was developed based on the NCEC Implementation guide (DoH, 2018). It outlines the actions required to implement each recommendation, who has lead responsibility for delivering the action, the timeframe for completion and the expected outcomes of implementation.

This National Clinical Guideline including the implementation plan should be reviewed by the multidisciplinary team and senior management in the hospital as it outlines the actions required to implement the recommendations.

The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline.

All medical staff with responsibility for the care of patients with gestational trophoblastic disease are required to:

- Comply with this National Clinical Guideline and any related procedures or protocols.
- Adhere to their code of conduct and professional scope of practice guidelines as appropriate to their role and responsibilities.
- Maintain their competency in the management and treatment of patients with gestational trophoblastic disease.

The National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this document. The guideline will also be available via the NCCP websites.

A summary of tools to assist in the implementation of this National Clinical Guideline is available in Appendix VI: Supporting tools.

3.12 Monitoring and Audit

It is important that both the implementation of the guideline and patient outcomes are monitored and audited to ensure that this guideline positively impacts on patient care. For audit criteria see Appendix VII: Monitoring and audit.

3.13 Recommendations for research

The following areas have been identified by the Guideline Development Group that require further research:

Recommendation 2.5.1.1

The guideline development group recommends that all women with suspected GTD should be registered with the National GTD Registry, Monitoring and Advisory Centre.

3.14 Systematic review of cost-effectiveness

As part of the systematic literature review any health economic literature identified in the literature search for each clinical question was included and critically appraised. Critical appraisal was carried out using the Consensus on Health Economic Criteria (CHEC)-list quality appraisal tool (Evers et al., 2005). The studies were also evaluated for applicability to the Irish setting using the International Society for Pharmacoeconomics (ISPOR) questionnaire (Jaime Caro et al., 2014).

A narrative synthesis of any cost-effectiveness literature identified was included in the evidence summary under the heading 'Resources and other considerations' and was taken into account when formulating recommendations.

3.15 Budget impact analysis

Any potential barriers or resource implications of implementing the recommendations were identified by the guideline development group during meetings to discuss and develop the clinical recommendations. The budget impact analysis for the resource implications identified for each clinical question is described in detail in Appendix IV: Economic assessment.

3.16 Plan to update this National Clinical Guideline

This guideline was issued in May 2022 and will be considered for review by the NCCP in three years. Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period or as a result of three year review will be noted in the guidelines section of the NCCP websites.

4.0 Appendices

Appendix I: Guideline Development Group terms of reference and logic model

Membership of the Guideline Development Group is outlined at the beginning of this document.

Terms of Reference

The terms of reference of the Guideline Development Group was to update National Clinical Guideline No. 13 - Diagnosis, staging and treatment of patients with gestational trophoblastic disease. To integrate the best current research evidence with clinical expertise and patient preferences and values. To provide guidance to clinicians in relation to the diagnosis, staging and treatment of patients.

Full terms of reference are available upon request.

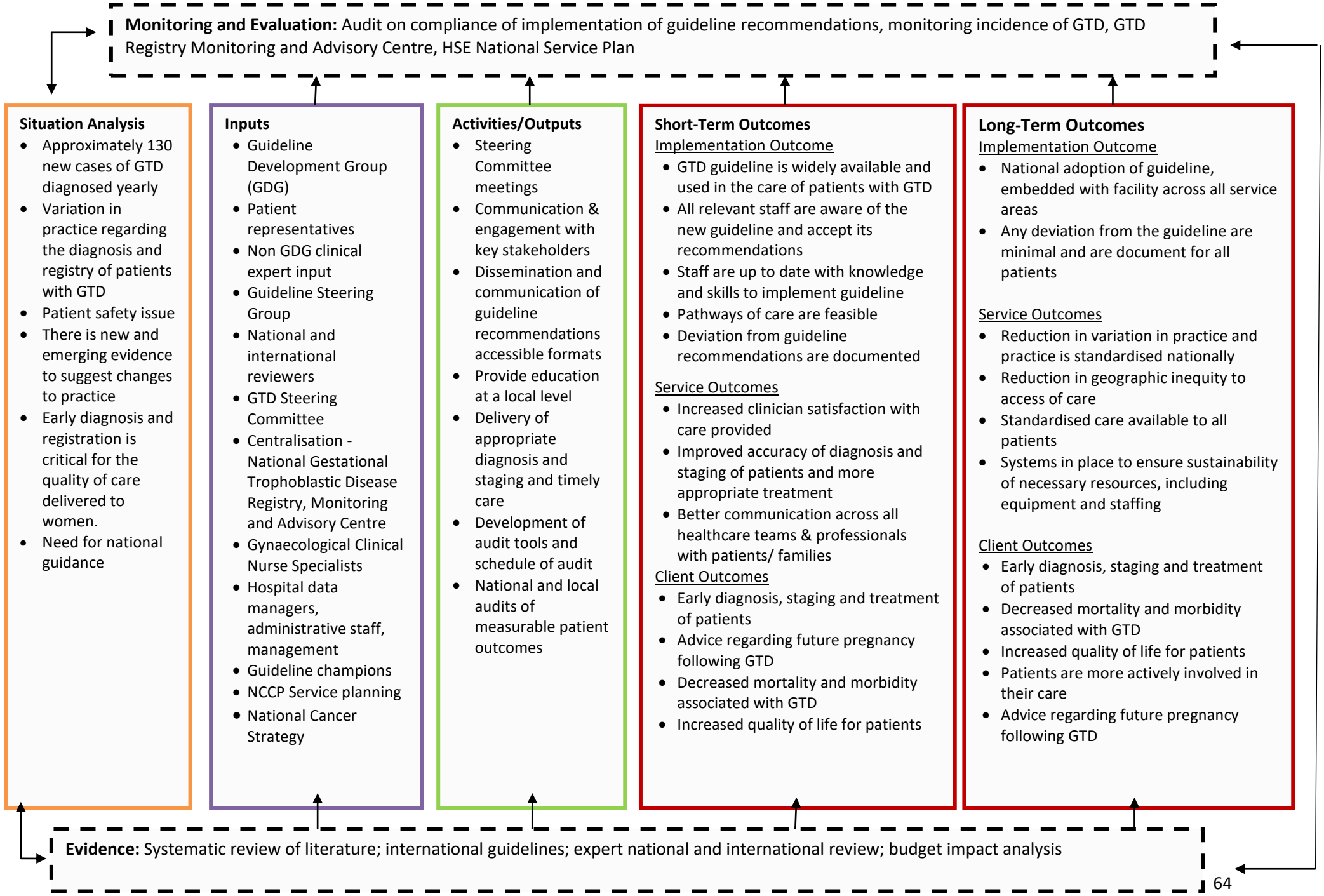
External Reviewers

The guideline development group would like to acknowledge Prof. Michael Seckl for sharing his expertise and commitment in reviewing this guideline.

Conflict of interest declarations

A conflict of interest form developed by the NCEC was signed by all Guideline Development Group members and reviewers. The Guideline Development Group was managed by the Chair to promote the highest professional standard in the development of this guideline. Where a conflict arises a Guideline Development Group member absents themselves from discussion pertaining to their area of conflict.

No conflicts were declared in the development of this national clinical guideline.


Monitoring and Evaluation: Audit on compliance of implementation of guideline recommendations, monitoring incidence of GTD, GTD Registry Monitoring and Advisory Centre, HSE National Service Plan
Situation Analysis
Approximately 130 new cases of GTD diagnosed yearly
Variation in practice regarding the diagnosis and registry of patients with GTD
Patient safety issue
There is new and emerging evidence to suggest changes to practice
Early diagnosis and registration is critical for the quality of care delivered to women.
Need for national guidance
Inputs
Guideline Development Group (GDG)
Patient representatives
Non GDG clinical expert input
Guideline Steering Group
National and international reviewers
GTD Steering Committee
Centralisation - National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre
Gynaecological Clinical Nurse Specialists
Hospital data managers, administrative staff, management
Guideline champions
NCCP Service planning
National Cancer Strategy
Activities/Outputs
Steering Committee meetings
Communication & engagement with key stakeholders
Dissemination and communication of guideline recommendations accessible formats
Provide education at a local level
Delivery of appropriate diagnosis and staging and timely care
Development of audit tools and schedule of audit
National and local audits of measurable patient outcomes
Short-Term Outcomes
Implementation Outcome
GTD guideline is widely available and used in the care of patients with GTD
All relevant staff are aware of the new guideline and accept its recommendations
Staff are up to date with knowledge and skills to implement guideline
Pathways of care are feasible
Deviation from guideline recommendations are documented
Service Outcomes
Increased clinician satisfaction with care provided
Improved accuracy of diagnosis and staging of patients and more appropriate treatment
Better communication across all healthcare teams & professionals with patients/ families
Client Outcomes
Early diagnosis, staging and treatment of patients
Advice regarding future pregnancy following GTD
Decreased mortality and morbidity associated with GTD
Increased quality of life for patients
Long-Term Outcomes
Implementation Outcome
National adoption of guideline, embedded with facility across all service areas
Any deviation from the guideline are minimal and are document for all patients
Service Outcomes
Reduction in variation in practice and practice is standardised nationally
Reduction in geographic inequity to access of care
Standardised care available to all patients
Systems in place to ensure sustainability of necessary resources, including equipment and staffing
Client Outcomes
Early diagnosis, staging and treatment of patients
Decreased mortality and morbidity associated with GTD
Increased quality of life for patients
Patients are more actively involved in their care
Advice regarding future pregnancy following GTD
Evidence: Systematic review of literature; international guidelines; expert national and international review; budget impact analysis

Appendix II: Systematic literature review protocol

National Cancer Control Programme

HSE Library Services
NCCP Guideline Development
www.hselibrary.ie

Literature searches to answer clinical questions identified by the relevant tumour group will be conducted using the following procedure. Questions should only be submitted if they have not been adequately answered in the guidelines adopted by the tumour group, or where guidelines need to be updated. Guidelines should be identified in consultation with library services.

Tumour Group	**1**	**PICO(T)**		Analyse the clinical question using PICO(T) and complete a Clinical Query Request form. See below Appendix 1: Clinical Query Request.
Tumour Group or Library Services	**2**	**Question Category**		Assign a question category, if appropriate: Therapy/Intervention □ Aetiology/Risk Factors □ Diagnosis □ Prognosis/Prediction □ Frequency/Rate □ Phenomena □ Other □
Library Services	**3**	**Literature Search**		Conduct searches of the following bibliographic databases in the order specified below using keywords implicit in the PICO(T) strategy and any identified subject headings:
		Cochrane	**3.1**	**Cochrane Library** Comprising: the Cochrane Database of Systematic Reviews; the Cochrane Central Register of Controlled Trials (Central); the Database of Abstracts of Reviews of Effects; the Health Technology Assessment Database; the NHS Economic Evaluation Database. Use MeSH and keyword searches to identify systematic reviews and other relevant studies.
		Point-of-Care	**3.2**	**Point-of-Care Reference Tools** One or more of the following point-of-care reference tools: BMJ Best Practice; DynaMed; UpToDate.
		Medline	**3.3**	**Medline** Use MeSH and keyword searches. Limit results using the 'Human' search filter. Unless otherwise specified by the tumour group or warranted by the specific clinical question, limit results to studies from the previous 5 years. Where appropriate, limit intervention questions according to the following priority: Medline clinical queries; Cochrane systematic reviews; other systematic reviews or meta-analyses; RCTs; systematic reviews of cohort or cross-sectional studies; cohort or cross-sectional studies; general Medline or other sources. Where appropriate, limit diagnosis, prognosis or aetiology questions according to the following priority: Medline clinical queries; systematic reviews of cohort or cross-sectional studies; cohort or cross-sectional studies; general Medline or other sources.
		Embase	**3.4**	**Embase** Repeat the Medline search strategy above using Embase, if available.

		Other Databases	3.5	**Other Bibliographic Databases** Repeat the Medline search strategy above using the Cumulative Index to Nursing and Allied Health Literature and/or PsycINFO, as appropriate.
		Other Sources	3.6	**Other Sources** Use any other sources for background or additional information, as appropriate. Other sources may include: PubMed, particularly for in-process or ahead-of-print citations; quality-assured, subject-specific Internet resources; clinical reference books; patient information materials; etc.
		Trial Registers	3.7	**Trial Registers** When a relevant trial is identified through searching the bibliographic databases, a search of trial registers should be carried out to identify any related trials which have been completed but whose findings have not been published or made available. The tumour group should be alerted to the presence of these unpublished trials. The following sources may be included:
			3.7.1	**ClinicalTrials.gov**: http://clinicaltrials.gov/
			3.7.2	**Cochrane Central Register of Controlled Trials (Central)**: http://www.thecochranelibrary.com/
			3.7.3	**EU Clinical Trials Register**: https://www.clinicaltrialsregister.eu/
			3.7.4	**International Prospective Register of Systematic Reviews (Prospero)**: http://www.crd.york.ac.uk/prospero/search.asp
			3.7.5	**WHO International Clinical Trials Registry**: http://apps.who.int/trialsearch/
Library Services	**4**	**Reference Management**		Retain an electronic record of the search strategy and all search results using the Zotero reference management utility.
Library Services	**5**	**Search Results**		Respond to the tumour group using the Clinical Query Response form to include: ▪ a copy of the search strategy ▪ bibliographic details of all search results identified ▪ optionally, a note of studies that seem to the librarian to be of particular relevance to the clinical question See below Appendix 2: Clinical Question Response.
Library Services	**6**	**Retracted Publications**	6.1	Set up an alert to review results lists returned to the tumour group to rapidly capture any articles that are subsequently retracted or withdrawn, and notify the tumour group accordingly.
Tumour Group or Library Services		**Retracted Publications**	6.2	Review all articles included in recommendations of the completed guideline to confirm that they have not been subsequently retracted or withdrawn.
Library Services	**7**	**Summary of Search Strategy**		A summary of the search strategy is included as an addendum to the completed guideline. Complete the Clinical Question: Summary of Search Strategy form and return to the tumour group. See below Appendix 4: Clinical Question: Summary of Search Strategy.

Clinical question request to library

Your Contact Details	
Name	
Job Title	
Work Address	
Telephone	
Email	
Employee Number	
Please state your clinical question	
… and list any relevant keywords	
… or (optional) enter keywords under the following headings (PICO)	
PICO	
Population/Problem	
Intervention/Indicator	
Comparator/Control	
Outcome	

Is your question specific to any of the categories below?		
GENDER	AGE GROUP	DATE OF PUBLICATION
Male □ Female □	Infant (0 – 23 months) □ Child (2 – 12 years) □ Adolescent (13 – 18 years) □ Adult (19 – 65 years) □ Aged (> 65 years) □	Current year only □ 0 – 5 years □ > 5 years □

Question Type	
Therapy/Intervention □	
Aetiology/Risk Factors □	
Diagnosis □	
Prognosis/Prediction □	
Frequency/Rate □	
Phenomena □	
Other □	
Additional Information	

Clinical question response

Dear _____,

Thank you for your email. Please see attached in response to your clinical query and, below, details of the search strategy applied to your question. If you wish to source any of the references contained in these results, or to search further, please do not hesitate to contact us.

Best wishes,

_____.

[ATTACH CLINICAL QUESTION REQUEST HERE]

Search Strategy		
Primary Database(s) Searched		
Search Strategy		
Other/Secondary Resources Searched		
Comments		
Contact		
Your Library Staff Contact		
Date		

Clinical question: summary of search strategy

Clinical Question		
PICO		
Population/Problem		
Intervention/Indicator		
Comparator/Control		
Outcome		
Is your question specific to any of the categories below?		
GENDER	AGE GROUP	DATE OF PUBLICATION
Male □ Female □	Infant (0 – 23 months) □ Child (2 – 12 years) □ Adolescent (13 – 18 years) □ Adult (19 – 65 years) □ Aged (> 65 years) □	Current year only □ 0 – 5 years □ > 5 years □
Question Type		
Therapy/Intervention □		
Aetiology/Risk Factors □		
Diagnosis □		
Prognosis/Prediction □		
Frequency/Rate □		
Phenomena □		
Other □		
Search Strategy		
Primary Database(s) Searched		
Search Strategy	[Copy of base Medline and/or PubMed search strategy HERE. Include subject headings and search hits].	
Other/Secondary Resources Searched		
Search Strategy: Other Resources	[Copy of other search strategies HERE. Include subject headings and search hits].	
Comments	[Short paragraph describing search].	
Date		

Appendix III: Details of consultation process

As part of the consultation process, the draft guideline was circulated for review to this list of groups, committees and organisations. The guideline was also available on the NCCP website so it was accessible to all who wished to comment and provide feedback.

Clinical leaders and healthcare managers	National Gynaecology Oncology Leads Group Masters of Maternity Hospitals HSE Clinical Programme in Surgery HSE Clinical Programme in Radiology HSE Clinical Programme in Pathology HSE Clinical Programme in Palliative Care HSE Clinical Programme in Medical management & pharmacological interventions HSE Clinical Programme in Obstetrics and Gynaecology HSE Clinical Programme in Primary Care HSE Clinical Programme in Acute Medicine HSE Clinical Programme in Anaesthesia HSE Clinical Programme in Critical Care HSE Clinical Programme in Emergency Medicine HSE Clinical Programme in Rare Diseases HSE Clinical Programme in Rehabilitation Medicine Older People Clinical Programme National Transport Medicine Programme CEOs of Hospital Groups CEOs of the Designated Cancer Centres CEOs of Cancer Network Hospital
National groups, organisations, faculties & committees	Faculty of Surgery Faculty of Radiology Faculty of Pathology Chairs of Obstetrics and Gynaecology Allied Health Professional Bodies: • Irish Nutrition & Dietetic Institute (INDI) • Irish Society of Chartered Physiotherapist • Association of Occupational Therapists of Ireland • Irish Association of Physicists in Medicine (IAMP) Irish Society for Medical Oncologists (ISMO) Irish Association for Nurses in Oncology (IANO) Irish College of General Practitioners (ICGP) Irish Association of Emergency Medicine Irish Association of Directors of Nursing and Midwifery Hospital Pharmacists Association of Ireland Oncology Pharmacists Special Interest Group National Screening Service Irish Association of Practice Nurses Association for improvement in Maternity Services
Patient support and advocacy groups	Irish Cancer Society Cancer Care West HSE Patient Forum Marie Keating Foundation Gary Kelly Cancer Support Centre Purple House Support Centre

	All Ireland Institute of Hospice and Palliative Care ASH Ireland The Irish Hospice Foundation The Irish Association for Palliative Care Miscarriage Association of Ireland Irish Association for Gynaecology Oncology (ISGO)
International Expert Review	Professor Michael Seckl, Charing Cross Hospital

Appendix IV: Economic assessment

Economic evidence summary

As part of the systematic literature review any health economic literature identified in the literature search for each clinical question was included and critically appraised. Critical appraisal was carried out using the Consensus on Health Economic Criteria (CHEC)-list quality appraisal tool (Evers et al., 2005). The studies were also evaluated for applicability to the Irish setting using the International Society for Pharmacoeconomics (ISPOR) questionnaire (Jaime Caro et al., 2014).

Only one cost-effectiveness analysis (Miller et al., 2017) was identified to address clinical question 2.4.2. A narrative synthesis of any cost-effectiveness literature identified was included in the evidence summary under the heading 'Resources and other considerations'.

Budget Impact Analysis

Any potential barriers or resource implications of implementing the recommendations were identified by the clinicians during meetings to discuss and develop the clinical recommendations. The potential barriers and resource implications that were identified by the guideline development group and expected to have a potential budget impact are described below.

Access to histopathological assessment

The issue of access to specialised pathological investigations (p57KIP2, immunohistochemistry/ploidy assessment/molecular analysis) was identified in clinical question 2.2.1 and 2.2.2.

In 2015 the NCCP GTD Steering Committee conducted a survey on access to specialised pathological investigations in laboratories nationally that deal with suspected molar pregnancies. This survey was repeated in 2019 by the pathology department of Cork University Hospital. It found a small number of laboratories did not currently have access to p57KIP2, but some were currently in the process of sourcing it.

The GTD Steering Committee will repeat this survey to verify all laboratories have access to p57KIP2. This is not expected to have an associated cost or budget impact as it is expected that all laboratories will now have access to p57KIP2. Pathways to other specialised tests will also be verified by the GTD Steering Committee.

Centralisation of serum hCG testing

The issue of centralisation of serum hCG testing was identified in clinical question 2.2.6, 2.2.7 and 2.4.5.

Implementation of a centralised national hCG assay testing service at CUH will help standardise follow-up care for women with GTD by use of a single reference interval across the country for the determination of hCG normalisation.

Centralisation of serum hCG testing will provide equity of access for all women with GTD to services routinely available at similar sized GTD specialist centres in the UK. It will support clinical decision making for women registered with the National GTD Registry, Monitoring and Advisory Centre as the service and clinical team are co-located at CUMH.

It is also expected to reduce patient waiting time by providing rapid hCG results using a CE marked assay in an accredited centre by experienced scientists cognisant of assay interference mechanisms. Centralisation of hCG testing will also facilitate audit and research to support tracking trends in disease presentation and service requirements.

The implementation plan and estimated costing for centralisation of hCG testing is outlined in the business case for a National hCG Diagnostic Service for Gestational Trophoblastic Disease. The business case outlines in detail

the proposal, capital requirements, risk assessment, cost and funding estimates and a cost-benefit analysis. The estimated cost of implementing a hCG diagnostic service is €1,500 per patient per annum, this represents outstanding value for a world class diagnostic service.

Funding for centralisation of serum hCG testing will be sought through the National Service Planning process.

Cost of serum hCG testing for patients
The issue of the cost of serum hCG testing for patients was identified in clinical question 2.2.2 and 2.4.1.

The guideline development group highlighted that for a small number of women hCG follow-up may have a personal financial implication for those women who currently attend their GP for follow-up serum hCG testing. The GTD Steering Committee will prepare a submission to the HSE Contracts Office to request a phlebotomy service in the community for GTD monitoring as a special item of service under the General Medical Service (GMS) contract.

It was agreed that a key priority of the NCCP GTD Steering Committee to implementing the recommendations was communication with GPs. This is outlined in detail in Appendix V: Implementation plan. It was agreed that the GTD Steering Committee should develop a comprehensive information booklet/letter for GPs. It is estimated that the development, design and printing of these booklets will cost €1,199.

Dissemination of this National Clinical Guideline
The issue of dissemination of the National Clinical Guideline was identified in clinical question 2.2.5 and 2.2.6. Dissemination of the guideline is not expected to have an associated cost or budget impact.

The National Clinical Guideline will be circulated and disseminated through the professional networks who were consulted on the development and review of this guideline. Please see Appendix III: Details of consultation process. The guideline will be officially launched and circulated to all relevant faculties and colleges for dissemination to their members.

The guideline will be available via the NCCP and CUH website. The NCCP will co-ordinate with HSE Communications to distribute, share and disseminate the guideline through the various media channels (Health Service News, Health Matters, and Twitter).

The implementation of the guideline will also be supported by communication, training and education. Potential dissemination and communication strategies:

- Promote through HSE/NCCP website and social media.
- Direct communication from NCCP Director/CCO/Acute Operations to hospital managers raising awareness and setting out expectations/ actions.
- Liaise with Faculties, Irish Cancer Society and relevant voluntary organisation to ensure guidelines are represented in their patient and public information.
- Included link to guidelines in NCCP email signatures.
- NCCP to create slide for inclusion in presentations by clinical leads, sub-group chairs, NCCP Director around published guidelines.
- Include discussion on implementation at guideline launch.

Appendix V: Implementation plan

Recommendation no.	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
Diagnosis 2.2.1.1 Histological assessment 2.2.2.2 p57KIP2,	**Barrier:** Access to specialised pathological investigations may be required in certain cases e.g. P57KIP2 immunohistochemistry/ploidy assessment/molecular analysis. **Enabler:** NCCP GTD Steering Committee	Verify laboratories pathways to timely access to specialised pathological investigations (p57KIP2 immunohistochemistry/ploidy assessment/molecular analysis.)	**NCCP** NCCP GTD Steering Committee (advised by pathology representatives)	X			**Outcome:** Laboratories have access to all relevant tests to enable efficient classification and treatment of molar pregnancies. **Verification:** Repeating of the survey carried out by CUH on access to specialised pathological investigations to ensure all relevant laboratories have access to tests.
Diagnosis 2.2.2.2 Diagnostic tests	**Barrier:** Cost of serum hCG testing for patients attending GP practices for hCG testing. **Enabler:** NCCP GTD Steering Committee	GP representative to be invited to be a member of the GTD Steering Committee GTD Steering Committee/GTD Centre to develop a comprehensive booklet/letter for GPs, to be sent to patients and to patient's GP. This will be sent to GP as soon as possible/with patients discharge letter. This	**NCCP** GTD Steering Committee/GTD Centre	X			**Outcome:** Patients undergo hCG testing that is carried out in an ISO15189 accredited laboratory that is CE marked for use in oncology. **Verification:** All women with a molar pregnancy have equitable access to hCG testing that is carried out in an ISO15189

Recommendation no.	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
		communication should also include information on/link to the National GTD website. Communication system in place between laboratories, GPs and the National GTD Registry, Monitoring and Advisory Centre to ensure all hCG reports provided to the GP (for woman with suspected GTD/GTD that are registered with the GTD Centre) should also be made available to the National GTD Registry, Monitoring and Advisory Centre GTD Steering Committee to prepare a submission to the HSE Contracts Office in order that hCG Testing for GTD would be considered for payment as a special item of service under the GMS scheme.					accredited laboratory that is CE marked for use in oncology.
Diagnosis 2.2.4.1 Registration	**Barrier:** Designated point of contact in maternity hospitals.	GTD Steering Committee to liaise with all maternity hospitals to request them to	**NCCP** GTD Steering Committee	X			**Outcome:** Each maternity hospital has a designated point of contact

Recommendation no.	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
	Enabler: GTD Steering Committee	appoint a designate person/point of contact for suspected cases of GTD. GTD Steering Committee to send regular reminders to maternity hospitals and the National Women and Infant's Health Programme to ensure that women with GTD/suspected GTD are registered with the National GTD Registry, Monitoring and Advisory centre. Pathologists to be reminded by the GTD Steering Committee to write specify the advice endorsed by the Faculty of Pathology "Patient registration with the National Gestational Trophoblast Disease Centre is recommended ".					with the National GTD Registry, Monitoring and Advisory Centre. **Verification:** All women with suspected or confirmed GTD are registered with the National GTD Registry, Monitoring and Advisory Centre.
Diagnosis 2.2.6.1 CHM, 2.2.6.2 PHM	**Barrier:** Dissemination of this National Clinical Guideline **Enabler:**	Development of a dissemination and communication plan for the guideline.	**NCCP** HSE	X			**Outcome:** All women with GTD are registered at the National GTD Registry, Monitoring and Advisory Centre and

Recommendation no.	Implementation barriers/enablers/gaps	Action/intervention/task to implement recommendation	Lead responsibility for delivery of the action	Timeframe for completion			Expected outcome and verification
				Year 1	Year 2	Year 3	
	GTD Steering Committee						undergo the correct management. **Verification:** Successful dissemination of the National Clinical Guideline.
Diagnosis 2.2.7.1 hCG centralisation	**Barrier:** Currently hCG centralisation is not available. **Enabler:** NCCP GTD Steering Committee	Development of a business case for a National hCG Diagnostic Service for the Gestational Trophoblastic Disease Centre. Develop a detailed pathway for implementation of hCG centralisation.	**NCCP** GTD Steering Committee (advised by Clinical Biochemistry/Chemical Pathology representatives)	X			**Outcome:** Timely access to hCG results for clinicians and patients. **Verification:** Successful implementation of a pathway for centralised testing.
Diagnosis 2.2.7.1 hCG centralisation	**Barrier:** hCG tumour marker code **Enabler:** NCCP GTD Steering Committee	GTD Steering Committee to liaise with HSE Clinical Programme for Pathology to request a hCG tumour marker code.	**NCCP** GTD Steering Committee	X			**Outcome:** Timely access to hCG results for clinicians and patients. **Verification:** Successful implementation of a hCG tumour marker code.

Appendix VI: Supporting tools

Downloading this guideline
This National Clinical Guideline will be available to download on the following websites:

NCCP: https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/

CUH: https://irelandsouthwid.cumh.hse.ie/gynaecology/gtd-centre/

Guides for health professionals are available here:
https://irelandsouthwid.cumh.hse.ie/gynaecology/gtd-centre/clinician-information/

Patient information booklets/leaflets are available here:
https://irelandsouthwid.cumh.hse.ie/gynaecology/gtd-centre/patient-information/

Appendix VII: Monitoring and audit

Implementation of the previous guideline

The setup of the National GTD Registry, Monitoring and Advisory Centre was guided by the preparation and development of the evidence based Gestational Trophoblastic Disease Diagnosis, Staging and Treatment Guideline which was prepared by the NCCP GTD Guideline Development Group and published by the National Clinical Effectiveness Committee. It was signed into practice by the Minister for Health on November 25th, 2015 http://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/gtd/

The National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre was established in May 2017 to monitor and co-ordinate the follow-up of women who have been diagnosed with a molar pregnancy. It is a service established by the HSE, the NCCP and CUMH. The Clinical Director of the National Gestational Trophoblastic Disease Registry, Monitoring and Advisory Centre is Dr John Coulter, Consultant Gynaecologist.

The primary objectives of the National GTD Registry, Monitoring and Advisory Centre are to:

- To register all women with GTD to ensure early detection of malignant change so that appropriate treatment can be instituted at the earliest possible time
- To monitor GTD patients for resolution, relapse or new episodes of the disease
- To provide accurate (expert) diagnosis for women
- To facilitate urgent management of patients requiring chemotherapy
- To provide Clinical Advice to Patients and Clinicians throughout the country on the management of GTD
- To provide regular reports (including an annual report) to NCCP and the HSE on GTD cases, treatment and outcome.

The registration of patients (following patient consent) has allowed centralised recording of hCG levels, which has ensured consistent monitoring and efficient management decisions, to improve clinical outcomes. More than 500 patients have been registered and all treated successfully by the Centre. The Centre was recognised in the recent HSE Excellence Awards where it received the *-Excellence in Quality Care Award* at the 2021 HSE Ceremony.

The guideline development group recommend that women with the following diagnoses should be registered and require follow-up:

- CHM
- PHM
- twin pregnancy with CHM or PHM
- limited macroscopic or microscopic molar change suggesting possible early CHM or PHM
- choriocarcinoma
- PSTT or ETT
- atypical placental site nodule
- atypical GTD suspected
- p57KIP2 discordant villi.

Once registered, the patient is contacted by the National GTD Registry, Monitoring and Advisory Centre and given further information/counselling about her diagnosis. A website is available for both clinicians and patients (https://irelandsouthwid.cumh.hse.ie/gynaecology/gtd-centre/about-gtd-centre/). The purpose of this website is to provide information to both clinicians and patients regarding the disease, early management of molar pregnancies/trophoblastic disease and the registration of patients with the National Gestational Trophoblastic Disease (GTD) Treatment and Advisory Centre at CUMH.

A number of supporting tools developed by the National GTD Registry, Monitoring and Advisory Centre which have been assessed by the National Adult Literary Agency (NALA) are listed in Appendix VI: Supporting tools.

Steering Committee

Prior to the setting up of the GTD centre an NCCP GTD Steering Committee was set up. The Steering Committee had its inaugural meeting in April 2015. The role of the Steering Committee is to provide overall governance on the set up and operation of the GTD Centre.

The responsibilities of the steering committee are as follows:

- Advise on the set up and operation of the National GTD Registry, Monitoring and Advisory Centre
- Provide strategic direction and oversight to the Centre to ensure that it meets its aim
- Provide support and advice on matters referred to the Committee by the Clinical Lead of the GTD centre
- Provide the Clinical Lead with advice and direction where appropriate in relation to priorities and direction.
- Provide advice and guidance on business issues facing the centre
- Approve plans for the centre and any deviations from them
- Meet quarterly or as required.

The Steering Committee for the setup of the GTD centre includes representatives of all relevant stakeholder including Institute of Obstetrics & Gynaecology, Medical Oncology, Nursing, Biochemistry, Histopathology, Hospital Management, ICT, Patient Representative, Informatics, Health Service Management and the NCCP.

Audit

A number of audits have been undertaken in co-operation with the NCCP GTD Steering Committee.

1. An audit was undertaken by the GTD Steering Committee in 2015 prior to the setup of the GTD Centre which had the objectives of assessing Irish laboratories access to tests and techniques in GTD diagnosis.

2. The above audit was followed up by a more comprehensive audit in 2019 - the National Trophoblastic Disease Audit by the Department of Histopathology in Cork CUMH. This audit has the following objectives:

a) Identify the numbers of products of conception (POCs) processed nationally
b) Identify rates of GTD diagnoses
c) Establish rates of disease registration with the National Gestational Trophoblastic Disease Centre (NGTDC)
d) Assess laboratories access to ancillary techniques in GTD diagnosis

3. A survey was recently carried out by the National Clinical Care Programme for Pathology in advance of this current GTD guideline update. This survey assessed the techniques and tests available for histological examination of products of conception, responsiveness to 14 day turnaround time and use of a hCG assay CE marked for oncology.

4. Also recently a survey (Joyce et al., 2022) was recently carried out by a member of the GTD Steering Committee to assess Irish women's experience of GTD. The initial results of this survey will be considered by the GTD Steering committee at their next meeting. This was a 27 item questionnaire that was prepared with advice from the GTD steering committee, patients, and nursing staff of the GTD centre. 518 questionnaires were issued and 215 were returned giving a response rate of 42%.

5. A Harmonisation Project in relation to hCG was also set up further to the establishment of the National GTD Centre. It included representatives from the clinical biochemistry laboratories and the Irish External Quality

Assessment Scheme (IEQAS) to agree a co-ordinated approach to the delivery and assessment of hCG. The performance of both hCG nationally in the laboratories that measure hCG was monitored through a national internal quality control (IQC) programme and an external quality assessment scheme (EQA).

Guidelines on all aspects of the measurement of hCG were developed in conjunction with an Expert Review Group representing the Laboratories and were communicated to all participating laboratories.

The results of all Audits are considered and discussed by the centre in co-operation with the Steering Committee of the GTD Centre with a view to improving and developing service delivery and care for patients.

Appendix VIII: Glossary of terms and abbreviations

Definitions within the context of this document

Choriocarcinoma	A malignant disease characterised by abnormal trophoblastic hyperplasia and anaplasia, absence of chorionic villi, hemorrhage, and necrosis with direct invasion into the myometrium and vascular invasion resulting in spread to distant sites. (Lurain, 2010)
Cohort study	A research study that compares a particular outcome (such as lung cancer) in groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke compared with those who do not smoke). (NCI dictionary)
Complete mole	Complete moles are diploid and androgenic in origin, hydatidiform mole with no evidence of fetal tissue. Complete moles usually (75–80%) arise as a consequence of duplication of a single sperm following fertilisation of an 'empty' ovum. Some complete moles (20–25%) can arise after dispermic fertilisation of an 'empty' ovum. (RCOG, 2010)
Epithelioid trophoblastic tumour	ETT is a rare variant of PSTT. It develops from neoplastic transformation of chorionic-type extra-villous trophoblast. ETT typically presents as a discrete, hemorrhagic, solid, and cystic lesion that is located either in the fundus, lower uterine segment, or endocervix. Like PSTT, it forms tumour nodules in the myometrium. (Berkowitz et al., 2015a)
Invasive mole	A benign tumour that arises from myometrial invasion of a hydatidiform mole via direct extension through tissue or venous channels. (Lurain, 2010)
Meta-analysis	A process that analyses data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself. (NCI dictionary)
Partial mole	Partial moles are usually (90%) triploid in origin, with two sets of paternal haploid genes and one set of maternal haploid genes. Partial moles occur, in almost all cases, following dispermic fertilisation of an ovum. Ten percent of partial moles represent tetraploid or mosaic conceptions. In a partial mole, there is usually evidence of a fetus or fetal red blood cells. (RCOG, 2010)
Placental site trophoblastic tumour	PSTTs are malignant and develop from extravillous, intermediate trophoblast. They are usually diploid and monomorphic. Microscopically, these tumours show tumour (PSTT) no chorionic villi and are characterised by a proliferation of mononuclear intermediate trophoblast cells with oval nuclei and abundant eosinophilic cytoplasm. (Berkowitz et al., 2015a)
Randomised trial	An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. (CEBM website)

Systematic review	The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardised methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results. (CEBM website)

Abbreviations

5-FU	5-Fluorouracil
ACT-D	Actinomycin-D
AGREE II	Appraisal of Guidelines for Research and Evaluation II
CEBM	Centre for Evidence-Based Medicine
CEO	Chief Executive Officer
CHM	Complete Hydatidiform Mole
CNS	Central Nervous System
CO	Cyclophosphamide and vincristine
CT	Computed tomography
CUH	Cork University Hospital
CUMH	Cork University Maternity Hospital
CXR	Chest X-ray
DoH	Department of Health
EBP	Evidence-Based Practice
EMA	Etoposide, methotrexate and actInomycin D
EMA/CO	Etoposide, methotrexate, actinomycin D plus cyclophosphamide and vincristine
EP	Etoposide and cisplatin
ESMO	European Society for Medical Oncology
ETT	Epithelioid trophoblastic tumour
FA	Folinic Acid
FAV	5-FU, actinomycin D, and vincristine
FIGO	International Federation of Gynecology and Obstetrics
G-CSF	Granulocyte-colony stimulating factor
GDG	Guideline Development Group
GMS	General Medical Service
GTD	Gestational Trophoblastic Disease
GTN	Gestational Trophoblastic Neoplasia
GUH	Galway University Hospital
hCG[2]	Human Chorionic Gonadotropin
HM	Hydatidiform Mole
HSE	Health Service Executive
ICGP	Irish College of General Practitioners
IM	Intramuscular
ISMO	Irish Society for Medical Oncologists
IV	Intravenous
MAC	Methotrexate, actinomycin D, cyclophosphamide or chlorambucil
MDT	Multi-disciplinary Team
MRI	Magnetic Resonance Imaging
NCCP	National Cancer Control Programme
NETDC	New England Trophoblastic Disease Centre
NHS	National Health Service
NMH	National Maternity Hospital
OS	Overall Survival
PET	Positron Emission Tomography
pGTN	Persistent Gestational Trophoblastic Neoplasia
PHM	Partial hydatidiform mole

[2] hCG - when discussing measurement of hCG in this guideline, the authors are referring to serum analysis unless otherwise stated.

PSTT	Placental site trophoblastic tumour
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
TAP	Thorax, abdomen and pelvis
TE/TP	Paclitaxel/cisplatin and paclitaxel/etoposide
US	Ultrasound
WHO	World Health Organisation

Appendix IX: Clinical questions in PICO format

Diagnosis

Clinical question 2.2.1 Should all women undergoing medical management of miscarriage have histopathology of products of conception to exclude trophoblastic disease?	
Population:	Women undergoing medical management of miscarriage
Intervention:	Histopathology of products of conception
Comparison:	-
Outcome:	To identify partial or complete molar pregnancy
Clinical question 2.2.2 For women with suspected molar pregnancy (suspected partial hydatidifrom mole [PHM], complete hydatidifrom mole [CHM] or in patients where molar pregnancy cannot be excluded), what diagnostic tests should be done to accurately diagnose partial or complete molar pregnancy?	
Population:	Women with suspected molar pregnancy
Intervention:	Diagnostic tests (ultrasound, hCG, histopathology, cytogenetics, p57)
Comparison:	
Outcome:	Accurately diagnose partial/complete molar pregnancy - sensitivity and specificity
Clinical question 2.2.3 For women where there is suspicion of partial or complete molar pregnancy who have an evacuation performed, in what time frame should the pathology report (post-evacuation) be available to the clinician?	
Population:	Women with suspected partial or complete molar pregnancy
Intervention:	Histopathological review
Comparison:	-
Outcome:	Time to report to clinician
Clinical question 2.2.4 Which patients with confirmed or suspected GTD should be registered with the National GTD Registry, Monitoring and Advisory Centre?	
Population:	Patients with a suspected partial hydatidifrom mole (PHM), complete hydatidifrom mole (CHM) or in patients where molar pregnancy cannot be excluded
Intervention:	Referral to the National GTD Registry, Monitoring and Advisory Centre
Comparison:	Management of GTD locally
Outcome:	Survival, adverse events, patient support and information
Clinical question 2.2.5 In patients with suspected GTD, how should human chorionic gonadotropin (hCG) be measured?	
Population:	Patients with suspected GTD
Intervention:	Measurement of hCG (platform, sample type)
Comparison:	-
Outcome:	Consistency of results, efficacy of the service, avoidance of unnecessary treatment, cost to the patient, geographical equity of access
Clinical question 2.2.6 For women with partial and complete molar pregnancy, what clinical and hCG monitoring protocol	

should be carried out to ensure they have been fully followed up and require no further therapy or monitoring?	
Population:	Women with partial or complete molar pregnancy
Intervention:	Monitoring investigation – hCG levels
Comparison:	-
Outcome:	Do not require further therapy or monitoring
Clinical question 2.2.7 In women with confirmed GTD should monitoring of hCG be centralised?	
Population:	Patients with suspected GTD
Intervention:	Measurement of hCG (platform, sample type, centralised service)
Comparison:	-
Outcome:	Consistency of results, efficacy of the service, avoidance of unnecessary treatment, cost to the patient, geographical equity of access

Staging

Clinical question 2.3.1 For women with Gestational Trophoblastic Neoplasia (GTN), what investigations should be done to accurately stage GTN?	
Population:	Women with GTN
Intervention:	Chest X-ray (CXR), liver ultrasound (US), transvaginal ultrasound (TVU), Magnetic Resonance Imaging (MRI) brain (if Lung metastases), Computed Tomography – Thorax, Abdomen and Pelvis (CT-TAP) (if abnormality on chest x-ray or liver ultrasound)
Comparison:	
Outcome:	To determine extent of disease To determine chemotherapy regimen
Clinical question 2.3.2 For women with GTN, what risk scoring system should be used to stage GTN?	
Population:	Women with confirmed GTN
Intervention:	Staging system
Comparison:	-
Outcome:	Accurate staging of GTN

Treatment

Clinical question 2.4.1 For women with GTN, what are the clinical indicators to diagnose GTN warranting chemotherapy?	
Population:	Women with GTN
Intervention:	Clinical indicators
Comparison:	-
Outcome:	Commencement of chemotherapy
Clinical question 2.4.2 For patients with low-risk (FIGO 0-6) GTN, what is the optimal first-line chemotherapy regimen?	
Population:	Women with GTN
Intervention:	Chemotherapy regimens

	- Methotrexate/Folinic Acid - Actinomycin D
Comparison:	-
Outcome:	5-year survival, Recurrence, Metastases Side-effects from chemotherapy, Toxicity
Clinical question 2.4.3 For women with high-risk (FIGO ≥7) GTN, what is the optimal first-line chemotherapy regimen?	
Population:	Women with GTN
Intervention:	Chemotherapy regimens - EMA-CO - EMA/EP chemotherapy - TE/TP chemotherapy
Comparison:	-
Outcome:	5-year survival, Recurrence, Metastases
Clinical question 2.4.4 For women with low-risk GTN undergoing chemotherapy (first-course), what is the recommended course of action for observing and managing bleeding?	
Population:	Women with GTN undergoing chemotherapy
Intervention:	Observation & management of bleeding
Comparison:	-
Outcome:	Optimum management
Clinical question 2.4.5 For women with GTN, what are the appropriate investigations to monitor response to chemotherapy and follow-up?	
Population:	Women with GTN
Intervention:	hCG levels
Comparison:	-
Outcome:	Response to chemotherapy and follow-up
Clinical question 2.4.6 For women with gestational trophoblastic neoplasia what are the indicators to determine switching treatments from first-line chemotherapy?	
Population:	Women with low-risk GTN undergoing first-line chemotherapy
Intervention:	Indicators - plateau in hCG - toxicity
Comparison:	-
Outcome:	Switch from first-line treatment
Clinical question 2.4.7 For women with low-risk gestational trophoblastic neoplasia who have not responded or have relapsed from single agent treatment (methotrexate or actinomycin D) or have relapsed following normalisation of hCG after completion of single agent treatment, what is the next line treatment? For women with high-risk GTN who have not responded to first-line treatment, what is second-line treatment?	
Population:	Women with low-risk invasive GTN who have not responded to single agent treatment or relapsed.

Intervention:	Next line treatment chemotherapy
Comparison:	-
Outcome:	5-year survival
Clinical question 2.4.8 For women with high-risk GTN who have not responded to first-line treatment, what is second-line treatment?	
Population:	Women with high-risk GTN who have not responded to first-line treatment
Intervention:	Second-line treatment chemotherapy
Comparison:	-
Outcome:	5-year survival
Clinical question 2.4.9 For women with GTN, who are acutely ill with liver, brain or lung metastasis at presentation, what is the optimum chemotherapy regimen?	
Population:	Women with GTN who are acutely ill with liver, brain or lung metastases
Intervention:	Management / treatment options - 2 days EP (Charing Cross protocol)
Comparison:	-
Outcome:	Survival

Appendix X: Levels of evidence and grading systems

2022 levels of evidence and grading systems

The Guideline Development Group assigned each recommendation a quality of evidence and strength of recommendation. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach provides an explicit system for rating the quality of evidence and whether the recommendation is strong or weak (Guyatt et al., 2008).

Quality of evidence

It is recognised that in guideline development that just assessing the level of evidence does not take into account the methodological quality of each individual study or the quality of the body of evidence as a whole (Harbour and Miller, 2001). The Guideline Development Group used the GRADE system which considers the following factors when classifying the quality of evidence; high, moderate or low (Guyatt et al., 2008):

- Study design
- Study design limitations
- Consistency of results
- Directness of the evidence
- Imprecision of results
- Reporting bias

Table 6 Quality of evidence adapted from GRADE working group 2013

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Strength of recommendation

There are two grades of recommendation: strong or weak. The strength of recommendation reflects the balance of the following items:

- The quality of the body of evidence
- The balance between benefit and harm to patient
- Patient preferences and values
- Resources/cost

Table 7 Strength of recommendation adapted from GRADE working group 2013

Strong	A strong recommendation is one for which the Guideline Development Group is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). Strong recommendations are not necessarily high priority recommendations. A strong recommendation implies that most or all individuals will be best served by the recommended course of action.
Weak	A weak recommendation is one for which the desirable effects probably outweigh

	80 the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but appreciable uncertainty exists. A weak recommendation implies that not all individuals will be best served by the recommended course of action. There is a need to consider more carefully than usual the individual patient's circumstances, preferences, and values. When there are weak recommendations caregivers need to allocate more time to shared decision making, making sure that they clearly and comprehensively explain the potential benefits and harms to a patient.

Good practice points

Good practice points were based on the clinical expertise of the Guideline Development Group.

Practical considerations around patient care

Practical considerations around patient care are statements developed with the patients that were involved in the development of the guideline on issues that were important to them with regards to their own experience of the diagnosis and staging of their cancer.

2015 grade of recommendations

For clinical questions and recommendations that have been retained from the 2015 guideline the following grades of recommendation apply.

Table 8 Levels of evidence for diagnostic studies for recommendations that have been retained from the 2015 guideline (Oxford Centre for Evidenced Based Medicine, 2009)

1a	Systematic review (with homogeneity*) of Level 1 diagnostic studies; clinical decision rule (CDR") with 1b studies from different clinical centres.
1b	Validating** cohort study with good reference standards""; or CDR tested within one clinical centre.
1c	Absolute SpPins (specificity) and SnNouts (sensitivity)"".
2a	Systematic review (with homogeneity*) of Level >2 diagnostic studies.
2b	Exploratory** cohort study with good reference standards; CDR after deviation, or validated only on split-samples§§§ or databases.
3a	Systematic review (with homogeneity*) of 3b and better studies.
3b	Non-consecutive study; or without consistently applied reference standards.
4	Case-control study, poor or non-independent reference standard.
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

" Clinical Decision Rule (these are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category).

** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An

exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

" " " Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

" " An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a negative result rules-out the diagnosis.

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Table 9 Grades of recommendations for diagnostic studies for recommendations that have been retained from the 2015 guideline (Oxford Centre for Evidenced Based Medicine, 2009)

A	Consistent level 1 studies.
B	Consistent level 2 or 3 studies; or Extrapolations from level 1 studies.
C	Level 4 studies; or Extrapolations from level 2 or 3 studies.
D	Level 5 evidence; or Troublingly inconsistent or inconclusive studies of any level.

Extrapolations are where data is used in a situation that has potentially clinically important differences than the original study situation.

Table 10 Levels of evidence for interventional studies for recommendations that have been retained from the 2015 guideline (Scottish Intercollegiate Guideline Network (SIGN), 2011)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies (e.g. case reports, case series).
4	Expert opinion.

Table 11 Grades of recommendations for interventional studies for recommendations that have been retained from the 2015 guideline (Scottish Intercollegiate Guideline Network (SIGN), 2011)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.

C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++.
D	Evidence level 3 or 4;or Extrapolated evidence from studies rated as 2+.

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

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