

Diagnosis, staging and treatment of patients with gestational trophoblastic disease

National Clinical Guideline No. 13

Summary

Guideline Development Group

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



Reference of National Clinical Guideline

National Clinical Guideline No. 13 should be referenced as follows:

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National Clinical Guideline No. 13 Summary.

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This Guideline Summary should be read in conjunction with the full version National Clinical Guideline.

The full version of this National Clinical Guideline is available at:

www.health.gov.ie/patient-safety/ncec and www.hse.ie/cancer

The complete list of references can be found in the full version of the National Clinical Guideline.

Notice to Health Professionals and Disclaimer

The Guideline Development Group's expectation is that health professionals will use clinical knowledge and judgement 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 judgement in such a decision must be clearly documented. Care options should be discussed with the patient, her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary.

National Clinical Effectiveness Committee

The National Clinical Effectiveness Committee (NCEC) was established as part of the Patient Safety First Initiative. The NCEC is a partnership between key stakeholders in patient safety. NCEC's mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit.

The aim of the suite of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence-based and consistent care across Irish healthcare services.

NCEC Terms of Reference

1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
3. Publish standards for clinical practice guidance.
4. Publish guidance for National Clinical Guidelines and National Clinical Audit.
5. Prioritise and quality assure National Clinical Guidelines and National Clinical Audit.
6. Commission National Clinical Guidelines and National Clinical Audit.
7. Align National Clinical Guidelines and National Clinical Audit with implementation levers.
8. Report periodically on the implementation and impact of National Clinical Guidelines and the performance of National Clinical Audit.
9. Establish sub-committees for NCEC workstreams.
10. Publish an Annual Report.

Information on the NCEC structure and NCEC documentation is available at:
<http://health.gov.ie/patient-safety/ncec/>

Using this National Cancer Control Programme National Clinical Guideline

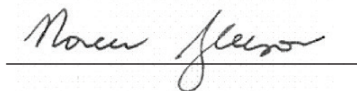
The National Cancer Control Programme (NCCP) is part of the Health Service Executive (HSE) and was established in 2007 to implement the recommendations of the National Cancer Strategy. The NCCP is responsible for national cancer control by helping to prevent cancer, treat cancer and increase survival and quality of life for those who develop cancer, by converting the knowledge gained through research and surveillance into strategies and actions. The need to follow evidence-based clinical guidelines covering a patient's journey from early detection, diagnosis, treatment, monitoring and end-of-life care is a key priority for the NCCP.

It is critical to have a range of health professionals working together to plan and deliver care for cancer patients. The target users of the guideline are the multidisciplinary clinical team caring for patients with gestational trophoblastic disease.

The development of this National Clinical Guideline by the NCCP would not have been possible without the enormous contribution of the members of the Guideline Development Group, the NCCP Guideline Steering Group and the reviewers. We are grateful for the commitment shown by all who contributed to the development of this guideline. In particular the invaluable input of the clinicians and the HSE/hospital librarians in this process is acknowledged and we thank them for giving generously of their time and expertise.

This Guideline Summary should be read in conjunction with the full version National Clinical Guideline.

The full version of this National Clinical Guideline is available at:
www.health.gov.ie/patient-safety/ncec and www.hse.ie/cancer



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1 Background

1.1 The rationale for a National Clinical Guideline

In 2006, the second national cancer strategy, *A Strategy for Cancer Control in Ireland* (DoHC, 2006), advocated a comprehensive cancer control programme. It was recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care.

The principal objective of developing these guidelines is to improve the quality of care received by patients. Additional objectives include:

- Improvements in the quality of clinical decisions
- Improvement in patient outcomes
- Potential for reduction in morbidity and mortality and improvement in quality of life
- Promotion of interventions of proven benefit and discouragement of ineffective ones, and
- Improvements in the consistency and standard of care.

1.2 Clinical impact of GTD

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 (Goldstein et al., 2014). 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).

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). According to figures from the Hospital In-Patient Enquiry (HIPE) database, in Ireland, on average, 105 new cases of GTD were diagnosed annually between the period 2005 to 2013. This guideline aims to improve the standard of clinical practice to ensure that young women affected by GTD are diagnosed promptly and receive the best available care.

1.3 Scope of the National Clinical Guideline, target population and target audience

1.3.1 Scope

This guideline focuses on the diagnosis, staging, and treatment of patients with GTD. This guideline does not include recommendations covering every aspect of diagnosis, staging, and treatment. This guideline focuses on areas of clinical practice:

- known to be controversial or uncertain
- where there is identifiable practice variation (2.2.3, 2.2.4, 2.3.1)
- where there is new or emerging evidence
- where guidelines have potential to have the most impact.

This guideline focuses solely on the clinical management of patients with GTD. The NCCP in partnership with the Irish Cancer Society has commenced a cancer survivorship programme.

1.3.2 Target population

Patients that are 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.

1.3.3 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, 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.

1.4 Levels of evidence and grading of recommendations

Tables 1 to 4 outline the categories used for levels of evidence and grading of recommendations.

Table 1 Levels of evidence for diagnostic studies (Oxford CEBM, 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 2 Grades of recommendations for diagnostic studies (Oxford CEBM, 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 3 Levels of evidence for interventional studies (SIGN grading system 1999-2012)

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 4 Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

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.

Good practice point

Recommended best practice based on the clinical experience of the Guideline Development Group.

2 National Clinical Guideline

2.1 Summary of clinical recommendations

Responsibility for implementation: 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.

There are various entry points for patients within the scope of this guideline.

2.2 Diagnosis

- 2.2.1.1** The histological assessment of material obtained from the medical or surgical management of all failed pregnancies (if available) is recommended to exclude trophoblastic disease (**Grade D**).
- 2.2.2.1** Ultrasound examination is helpful in making pre-evacuation diagnosis but the definitive diagnosis is made by histological examination of the products of conception (**Grade C**).
- 2.2.3.1** It is recommended that in all cases of suspected molar pregnancy, the preliminary pathology report should ideally be available to the clinician within 14 days (**Grade D**).
- 2.2.4.1** The guideline development group recommends that a National GTD Registry, Monitoring and Advisory Centre should be established for all cases of gestational trophoblastic disease (GTD) (**Grade D**).
- 2.2.4.2** The management of complicated cases should be discussed with the National GTD Registry, Monitoring and Advisory Centre clinical lead (**Grade D**).
- 2.2.5.1** For patients with complete hydatidiform mole serum human chorionic gonadotropin (hCG) is monitored weekly until normalisation for three weeks.
 - If this occurs within eight weeks 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 (**Grade C**).
- 2.2.5.2** For patients with partial hydatidiform mole the serum hCG should be monitored weekly until normalisation and one further confirmatory hCG measurement is performed 4 weeks later. If that confirmatory hCG is normal then follow up is complete (**Grade D**).

2.3 Staging

- 2.3.1.1** Women with gestational trophoblastic neoplasia (GTN) should have hCG, pelvic ultrasound, CT scan of abdomen & pelvis, and a chest x-ray (**Grade C**).
- 2.3.1.2** If metastases are present on chest x-ray a CT scan of the thorax and an MRI of the brain should be performed (**Grade C**).
- 2.3.2.1** Women with GTN (invasive mole, choriocarcinoma) should be assigned a FIGO score to direct management decisions of chemotherapy regimens (**Grade B**).

2.4 Treatment

- 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,
 - Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities of >2cm on chest x-ray,
 - Serum hCG of $\geq 20,000$ IU/l more than four weeks after evacuation, because of the risk of uterine perforation,
 - Raised hCG six months after evacuation even if still falling (**Grade C**).
- 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. In most European centres, methotrexate with folinic acid is preferred because it is less toxic than methotrexate alone or single-agent actinomycin D (**Grade C**).

- 2.4.2.2** Chemotherapy for low-risk disease should be continued for three cycles of maintenance treatment after hCG normalisation **(Grade C)**.
- 2.4.3.1** Patients with a FIGO score of ≥ 7 should receive multi-agent chemotherapy and most centres now use EMA/CO (Etoposide, methotrexate, actinomycin D plus cyclophosphamide and vincristine), as it is highly effective, easy to administer and relatively non-toxic **(Grade B)**.
- 2.4.3.2** Early deaths in ultra high-risk GTN can be reduced by induction therapy with etoposide and cisplatin. Such patients may also benefit from substitution of EMA/CO with EP/EMA (Etoposide and cisplatin plus etoposide, methotrexate, actinomycin D) **(Grade C)**.
- 2.4.4.1** For women with low-risk GTN undergoing first-line chemotherapy, the first \pm second course of chemotherapy should be administered as an in-patient at a centre with medical oncology, gynaecological services and interventional radiology **(Grade C)**.
- 2.4.5.1** Monitoring during treatment low-risk: Patients should have human chorionic gonadotropin levels monitored twice a week during treatment **(Grade C)**.
- 2.4.5.2** Monitoring during treatment high-risk: Patients with high-risk disease should have maintenance 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 **(Grade B)**.
- 2.4.5.3** Follow-up post treatment: After remission is achieved, serum hCG should be measured fortnightly until monitoring has shown one year of normal hCG levels **(Grade C)**.
- 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 weekly measurements a week apart **(Grade C)**.
- 2.4.7.1** For women with low-risk GTN who have not responded or have relapsed from single-agent treatment (methotrexate or actinomycin D), the next line of treatment is combination chemotherapy with EMA/CO **(Grade B)**.
- 2.4.8.1** For women with high-risk GTN who have not responded or have relapsed from first-line treatment, acceptable regimens include EP/EMA and TE/TP (Paclitaxel/cisplatin and paclitaxel/etoposide) **(Grade C)**.
- 2.4.9.1** Emergency Treatment - In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EMA/CO or EP/EMA at a later point **(Grade C)**.
- 2.4.9.2** Hepatic metastases - In patients who are acutely unwell from liver disease emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. Patients with hepatic metastases at presentation should commence therapy using EP/EMA protocol. Given the rarity of this condition each individual case should be discussed with International experts. **(Grade C)**.
- 2.4.9.3** Cerebral metastases - In patients who are acutely unwell from CNS emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to high dose EMA/CO at a later point using an increased methotrexate dose (1gm/m²) combined with longer FA rescue. CNS dose EMA/CO chemotherapy is continued for eight weeks after the hCG normalisation. In emergency situations with cerebral metastases, high-dose dexamethasone is given followed by two day EP as above. Given the rarity of this condition each individual case should be discussed with International experts. **(Grade C)**.
- 2.4.9.4** Hepatic and synchronous cerebral metastases - In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. 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. Given the rarity of this condition each individual case should be discussed with International experts. **(Grade C)**.

Good practice points

Recommended best practice based on the clinical experience of the Guideline Development Group.

2.2 Diagnosis

Responsibility for the implementation of recommendations

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?

Evidence statement

The evidence for this question comes from two guidelines which state that histopathology of products of conception should be performed in all cases of surgical and medical management of miscarriage and spontaneous miscarriage (RCOG, 2010; RCOG, 2006).

Women who miscarry at home and are admitted to hospital should be advised to take with them any tissue passed so that histological examination can be arranged. The attending practitioner should arrange for the appropriate laboratory examination (RCOG, 2006).

Histopathology of products of conception enables earlier accurate diagnosis of trophoblastic disease.

Recommendation 2.2.1.1	Grade
The histological assessment of material obtained from the medical or surgical management of all failed pregnancies (if available) is recommended to exclude trophoblastic disease.	D

Clinical question 2.2.2

For women with suspected molar pregnancy, what diagnostic tests should be done to accurately diagnose partial or complete molar pregnancy?

Evidence statement

There is international consensus that for women with suspected molar pregnancy further tests should be done and that histopathology is the gold standard (RCOG, 2010; Mangili et al., 2014).

In the largest series of more than 1000 patients with 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; Kirk et al., 2007). (Shanbhogue et al., 2013)

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.

The diagnosis of hydatidiform moles is established by:

- History
 - Clinical examination
 - Ultrasound examination
 - Serum hCG (human chorionic gonadotropin) levels
 - Histopathological examination
 - Cytogenetic and molecular biological examination if indicated.
- (Sasaki, 2003)

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.

Recommendation 2.2.2.1	Grade
Ultrasound examination is helpful in making pre-evacuation diagnosis of partial or complete molar pregnancy but the definitive diagnosis is made by histological examination of the products of conception.	C

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 is recommended.

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?

Evidence statement

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) 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). 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.

Recommendation 2.2.3.1	Grade
It is recommended that in all case of suspected molar pregnancy, the preliminary pathology report should ideally be available to the clinician within 14 days.	D

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 is recommended.

Clinical question 2.2.4

For women with gestational trophoblastic disease should management be centralised to a specialised centre(s) to ensure optimum outcome?

Evidence statement

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 centralised registry is necessary for the registration of all cases of GTD and monitoring of hCG follow-up. Care is optimised when management is centralised. The guideline development group recommends that there should be a maximum of two centres. All patients with hydatidiform mole should be registered and treated in conjunction with a specialist centre for hCG surveillance, preferably one that is coordinated nationally.

In 2013, approximately 86 patients gave rise to 195 discharges with a primary diagnosis of hydatidiform mole, malignant neoplasm of placenta or neoplasm of placenta of uncertain origin, to hospitals in the Irish public system according to data on incidences from the HIPE system.

A National GTD Registry, Monitoring and Advisory Centre for patients with GTD is currently being established in Ireland to register and audit all GTD referrals. All patients with GTD should be registered with the national GTD centre to allow centralised recording of hCG levels. The National MDT will notify the patients' treating clinician if further intervention/treatment is needed following hCG monitoring.

Recommendation 2.2.4.1	Grade
The guideline development group recommends that a National GTD Registry, Monitoring and Advisory Centre should be established for all cases of GTD.	D
Recommendation 2.2.4.2	Grade
The management of complicated cases should be discussed with the National GTD Registry, Monitoring and Advisory Centre clinical lead.	D

Clinical question 2.2.5

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

Evidence statement

There are a number of different protocols for the follow-up of hCG levels (Charing Cross, 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)

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 3). The current protocol is consistent with international best practice and is chosen for consistency.

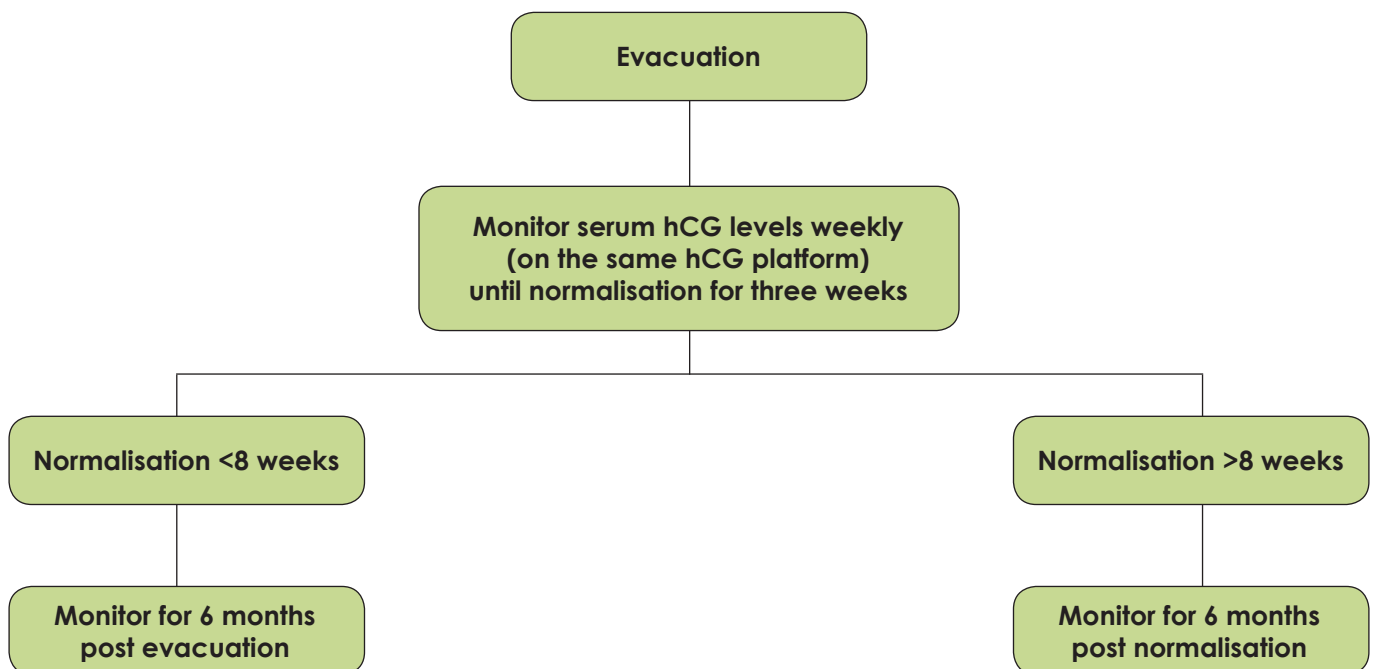


Figure 1 The current protocol for monitoring hCG levels in women with complete molar pregnancy

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. 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 (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.

Recommendation 2.2.5.1	Grade
<p>For patients with complete hydatidiform mole serum hCG is monitored weekly until normalisation for three weeks.</p> <ul style="list-style-type: none"> - If this occurs within eight weeks 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. 	C

Recommendation 2.2.5.2	Grade
<p>For patients with partial hydatidiform mole the serum hCG should be 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.</p>	D

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 and the pregnancy progresses as per any normal 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 post-natally regardless of the outcome of pregnancy.

Good practice point

Normal hCG is defined as 0-5 IU/l depending on which hCG platform is used.

2.3 Staging

Responsibility for the implementation of recommendations

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?

Evidence statement

Gestational trophoblastic neoplasia (GTN) includes: invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). In the absence of tissue for a definitive histopathologic diagnosis, GTN is diagnosed as a result of persistent elevation of hCG after evacuation of a molar pregnancy. (Berkowitz et al., 2015a)

Staging investigations and treatment stratification after a molar pregnancy

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. (Seckl et al., 2013)

Ultrasound is performed to rule out pregnancy in all patients. Once pregnancy is ruled out an expert gynecological ultrasound (a specialised Doppler ultrasound of the uterus and uterine artery) or a computed tomography (CT) scan should be performed in order to accurately stage GTN. It is reasonable in the Irish context in the absence of an expert gynecological ultrasound to perform a CT scan of the abdomen and pelvis due to the transferability, reliability and reproducibility of CT scans (figure 4).

CT of the chest is not required if the chest X-ray (CXR) findings are normal, since discovery of micrometastases, which may be seen in approximately 40% of patients, does not influence outcome (Darby et al., 2009). However, if lesions are noted on CXR, magnetic resonance imaging (MRI) of the brain and CT body are indicated to exclude more widespread disease involving, for example, the brain or liver, which would significantly alter management. (Seckl et al., 2013)

All patients should have a baseline chest radiograph to evaluate for lung metastases rather than CT, since a chest radiograph, not CT, is the basis for International Federation of Gynecology and Obstetrics (FIGO) staging. (Berkowitz et al., 2015a)

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 chest and abdomen, MRI of the brain and pelvis, a Doppler ultrasound of the 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. Some investigators have recently started using positron emission tomography/computed tomography (PET-CT) imaging, but experience is still quite limited. It appears that this imaging modality is more helpful in relapsed disease to identify sites for resection and, as with other cancers, is prone to both false-positive and false-negative results (Seckl et al., 2010). (Seckl et al., 2013)

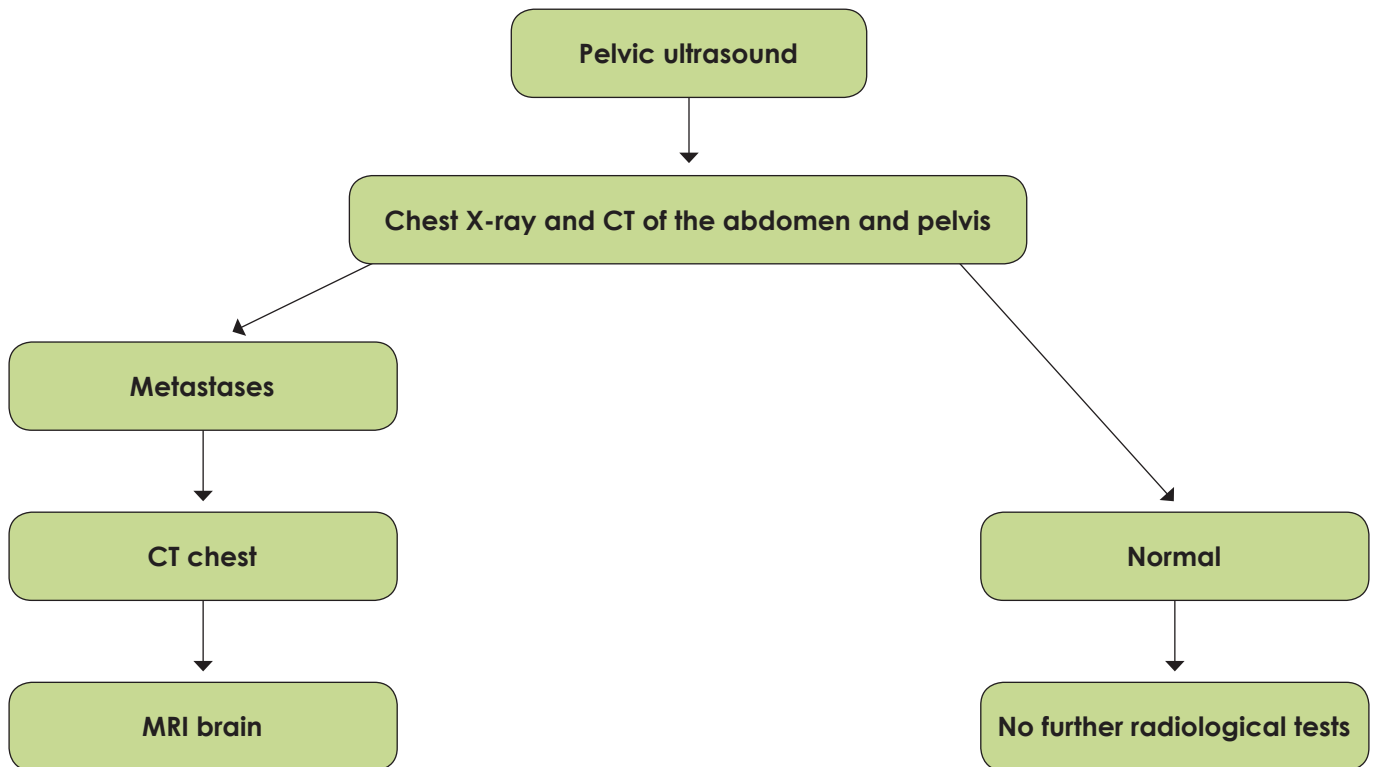


Figure 2 Radiological investigations for patients with GTN following a HM on hCG surveillance

Recommendation 2.3.1.1	Grade
Women with GTN should have hCG, pelvic ultrasound, CT scan of abdomen & pelvis, and a chest x-ray.	C

Recommendation 2.3.1.2	Grade
If metastases are present on chest x-ray a CT scan of the thorax and an MRI of the brain should be performed.	C

Good practice point
Investigation and management decisions should be performed by experienced professionals in this area.

Clinical question 2.3.2

For women with gestational trophoblastic neoplasia (GTN), what risk scoring system should be used to stage GTN?

Evidence statement

The International Federation of Gynecology and Obstetrics (FIGO) reports data on GTN using anatomic staging systems (Table 5) and prognostic scoring (Table 6) (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 5 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 6 Modified WHO prognostic scoring system as adapted by FIGO (2009)

Prognostic Factor	Scores			
	0	1	2	4
Age	<40	≥ 40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4-6	7-12	>12
Pretreatment 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	≥ 5 cm	–
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 (Seckl et al., 2013, Biscaro et al., 2015).

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

Responsibility for the implementation of recommendations

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 gestational trophoblastic neoplasia, what are the clinical indicators to diagnose GTN warranting chemotherapy?

Evidence statement

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. (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., 2012). However these decisions must be made on an individual patient basis following consultation with clinicians experienced in GTN management.

UK indications for chemotherapy following the diagnosis of GTN:

- Plateaued or rising hCG after evacuation*,
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage,
- Histological evidence of choriocarcinoma,
- Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities larger than 2 cm on chest radiograph. (Seckl et al., 2013)

- 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,
 - Women with a raised hCG six months after evacuation, even when hCG still decreasing.

Recommendation 2.4.1.1	Grade
Indications for chemotherapy following diagnosis of GTN: <ul style="list-style-type: none"> • Plateaued or rising hCG after evacuation*, • Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage, • Histological evidence of choriocarcinoma, • Evidence of metastases in the brain, liver, or gastrointestinal tract, or radiological opacities of >2 cm on chest x-ray, • Serum hCG of ≥20,000 IU/l more than four weeks after evacuation, because of the risk of uterine perforation, • Raised hCG six months after evacuation even if still falling. 	C

* 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.

Clinical question 2.4.2

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

Evidence statement

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., 2009). Consequently, a new larger international randomised trial has recently commenced comparing the more commonly used methotrexate regimens in Europe and many parts of the world and some centres elsewhere [methotrexate 0.4 mg/kg (maximum 25 mg) IV d1–5 every 2 weeks] (Lurain et al., 2012) with actinomycin-D (1.25 mg/m² IV every 2 weeks). Importantly, patients failing first-line therapy, usually because of resistance, can be easily salvaged 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. (Seckl et al., 2013)

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). (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.

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. In contrast, the Sheffield unit only gives CNS therapy to those with proven CNS metastases (Charing Cross, 2015).

Recommendation 2.4.2.1	Grade
Patients with a FIGO score of 0-6 can be treated with either single-agent methotrexate with or without folinic acid, or actinomycin D. In most European centres, methotrexate with folinic acid is preferred because it is less toxic than methotrexate alone or single-agent actinomycin D.	C

Recommendation 2.4.2.2	Grade
Chemotherapy for low-risk disease should be continued for three cycles of maintenance treatment after hCG normalisation.	C

Good practice point
In women with GTN, for whom fertility is not a clinical issue, hysterectomy may be a potential treatment option instead of chemotherapy as initial treatment.

Clinical question 2.4.3**For women with high-risk (FIGO ≥ 7) GTN what is the optimal first-line chemotherapy regimen?****Evidence statement**

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 .

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 EMA treatment. In contrast the Sheffield unit only gives CNS therapy to those with proven CNS metastases. They do a brain CT (computed tomography) and a CSF (cerebral spinal fluid) hCG in their 'high-risk' patients and only if positive give CNS therapy with intrathecal and intravenous methotrexate. (Charing Cross, 2015)

Recommendation 2.4.3.1	Grade
Patients with a FIGO score of ≥ 7 should receive multi-agent chemotherapy and most centres now use EMA/CO, as it is highly effective, easy to administer and relatively non-toxic.	B

Recommendation 2.4.3.2	Grade
Early deaths in ultra high-risk GTN can be reduced by induction therapy with etoposide and cisplatin. Such patients may also benefit from substitution of EMA/CO with EP/EMA.	C

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 national MDT.

Clinical question 2.4.4

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

Evidence statement

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 & 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, 2015)

Recommendation 2.4.4.1	Grade
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.	C

Clinical question 2.4.5

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

Evidence statement**Monitoring response to chemotherapy – Low-Risk**

Patients should have hCG levels monitored twice a week during treatment. 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 (Lybol et al., 2012). (Seckl et al., 2013)

Monitoring response to chemotherapy – High-Risk

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). (Seckl et al., 2013)

Follow-up of patients post chemotherapy

After remission is achieved, serum hCG should be measured fortnightly until monitoring has shown one year of normal hCG levels. Some centres e.g. Charing Cross, continue bi-annual titers indefinitely for high-risk individuals. Subgroups that might fit into this high-risk category include women with extreme treatment resistance who required multiple regimens of combination therapy, those with advanced stage choriocarcinoma, particularly with chemoresistance, and patients who have late recurrences. (Garner, 2013)

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

Recommendation 2.4.5.1	Grade
Monitoring during treatment low-risk: Patient should have human chorionic gonadotropin (hCG) levels monitored twice a week during treatment.	C
Recommendation 2.4.5.2	Grade
Monitoring during treatment high-risk: Patients with high-risk disease should have maintenance 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.	B
Recommendation 2.4.5.3	Grade
Follow-up post treatment: After remission is achieved, serum hCG should be measured fortnightly until monitoring has shown one year of normal hCG levels.	C

Good practice point

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

Clinical question 2.4.6

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

Evidence statement

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 & Nejad, 2005). (Biscaro et al., 2015)

Resistance to chemotherapy and recurrent disease are more frequent in patients with high-risk GTN (Berkowitz & 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	Grade
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.	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 to 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 of treatment?

Evidence statement

The next line of treatment is determined by the patient's current hCG levels, with those with hCG levels <300 IU/l receiving single-agent Actinomycin-D and those with hCG levels of >300 IU/l commencing on EMA-CO (Seckl et al., 2013).

In a recent study, Sita-Lumsden et al. (2012) demonstrated that a higher cut-off value of 300 IU/l produced an overall second-line actinomycin-D success rate of 94% that compares favourably with the 87% reported when the cut-off value was 100 IU/l.

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 & 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 & Berkowitz, 2012). (Alazzam, 2012)

In Ireland it is current practice to use EMA/CO as first-line combination therapy. Patients should be treated under the care of a medical oncologist with experience in the treatment of GTN.

A recent 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)

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 EMA treatment. In contrast the Sheffield unit only gives CNS therapy to those with proven CNS metastases. They do a brain CT scan and measure CSF hCG in their 'high-risk' patients and only if positive give CNS therapy with intrathecal and intravenous methotrexate (Charing Cross, 2015).

Recommendation 2.4.7.1	Grade
For women with low-risk GTN who have not responded or have relapsed from single-agent treatment (methotrexate or actinomycin D), the next line of treatment is combination chemotherapy with EMA/CO.	B

Clinical question 2.4.8

For women with high-risk GTN who have not responded or have relapsed from first-line treatment, what is second-line of treatment?

Evidence statement

In women with high-risk GTN who have not responded or have relapsed from 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 demonstrated 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). In three series of EMA/EP salvage treatment following EMA/CO treatment failure, cure rates of 75% (nine out of 12 women; Newlands 2000) 66.6% (12 out of 18 women; Mao 2007) and 84.9% (11 out of 13 women; Lu 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 2005; Lurain 2005; Seckl 2010). (Alazzam et al., 2012)

An alternative to EP/EMA 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., 2012). A randomised trial comparing these regimens is being developed (Seckl et al., 2013).

Another approach in patients with refractory disease involves high-dose chemotherapy with peripheral stem-cell transplantation. Cures are not common (El-Helw et al., 2005). (Seckl et al., 2013)

This approach should only be undertaken after expert advice has been sought internationally.

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 EMA treatment. In contrast the Sheffield unit only gives CNS therapy to those with proven CNS metastases. They do a brain CT scan and measure CSF hCG in their 'high-risk' patients and only if positive give CNS therapy with intrathecal and intravenous methotrexate (Charing Cross, 2015).

Recommendation 2.4.8.1	Grade
For women with high-risk GTN who have not responded or have relapsed from first-line treatment, acceptable regimens include EP/EMA and TE/TP.	C

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?

Evidence statement

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

Emergency treatment

In patients who are acutely unwell from liver or CNS (central nervous system) disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP. This can be repeated weekly and then altered to EMA/CO or EP/EMA at a later point. (Charing Cross, 2015)

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 should commence therapy using EP/EMA protocol. (Charing Cross, 2015)

Research by Barber et al. (2014) on patients with hepatic metastases revealed that 82% experienced a complete response to EMA/CO versus only 17% experiencing a complete response to other types of chemotherapy (Methotrexate, ACT-D, or MAC) ($P = 0.035$).

Cerebral metastases

The Charing Cross hospital's treatment for this is the high dose EMA/CO, using an increased methotrexate dose (1gm/m²) combined with longer folinic acid (FA) rescue. CNS dose EMA/CO chemotherapy is continued for eight weeks after the human chorionic gonadotropin (hCG) normalisation. Intrathecal methotrexate is also given as 12.5mg +15mg FA on the CO week until serum hCG is normal at which point it is discontinued.

In emergency situations with cerebral metastases, hi-dose dexamethasone is given followed by two day EP as above. (Charing Cross, 2015)

Hepatic and synchronous cerebral metastases

In patients with liver and brain metastases the treatment used should be as follows:

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/m ² in 1000ml normal saline over 24hrs IV
Week 1	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 3-4 days every week in between day 1 and 8 and day 8 and 1.

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, 2015, 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, 2015)

Recommendation 2.4.9.1	Grade
<p><u>Emergency treatment</u> In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EMA/CO or EP/EMA at a later point.</p>	C
Recommendation 2.4.9.2	Grade
<p><u>Hepatic metastases</u> In patients who are acutely unwell from liver disease emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. Patients with hepatic metastases at presentation should commence therapy using EP/EMA protocol. Given the rarity of this condition each individual case should be discussed with international experts.</p>	C
Recommendation 2.4.9.3	Grade
<p><u>Cerebral metastases</u> In patients who are acutely unwell from CNS emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to high dose EMA/CO at a later point using an increased methotrexate dose (1gm/m²) combined with longer FA rescue. CNS dose EMA/CO chemotherapy is continued for eight weeks after the hCG normalisation. In emergency situations with cerebral metastases, hi-dose dexamethasone is given followed by two day EP as above. Given the rarity of this condition each individual case should be discussed with international experts.</p>	C
Recommendation 2.4.9.4	Grade
<p><u>Hepatic and synchronous cerebral metastases</u> In patients who are acutely unwell from liver or CNS disease and particularly those at risk of respiratory failure, emergency chemotherapy can be started with two day EP (E 100mg/m² D1+2, P 20mg/m² D1+2). This can be repeated weekly and then altered to EP/EMA at a later point. 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. Given the rarity of this condition each individual case should be discussed with international experts.</p>	C

3**National Clinical Guideline development process****3.1 Objectives of the National Clinical Guideline**

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 research evidence in conjunction with clinical expertise
- Developed using a clear evidence-based internationally used methodology.

3.2 Methodology and literature review

The methodology for the development of the guideline was designed by a research methodologist in NCCP and is based on the principles of Evidence-Based Practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual for guideline development.

The first step in guideline development was to identify areas of new and emerging evidence or areas where there was variance in practice. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.

The literature was searched based on the hierarchy of evidence. The evidence which addressed each clinical question, both from international guidelines and primary literature, was extracted into evidence tables. Recommendations were formulated through a formal structured process. A 'considered judgment form' (adapted from SIGN; see NCCP Methodology Manual 2014) was completed for each clinical question.

3.3 Financial implications of GTD

The establishment of the National GTD Registry, Monitoring and Advisory Centre will have the potential to identify the volume of patients with GTD in the country, which will inform costs. Many recommendations in this guideline represent current standard practice and are therefore cost neutral. However, the GDG has identified the areas that require change to ensure full implementation of the guideline. The potential resource implications of applying these recommendations have been considered. See Appendix 11 of the full guideline for Budget Impact Assessment.

3.4 Patient advocacy

The views and preferences of the target population were sought by inviting patient advocacy groups (HSE Patient Forum, Irish Cancer Society, Cancer Care West, Marie Keating Foundation, Gary Kelly Cancer Support Centre, Bray Cancer Support Centre, and The Miscarriage Association of Ireland) to engage in the National Stakeholder Review process.

3.5 National stakeholder review and international expert review

The draft guideline was signed off by the entire GDG, the wider NCCP Gynaecology Tumour Group, and the NCCP Guideline Steering Group before going to national stakeholder review. A full list of those invited to review this guideline is available in the full guideline.

The amended draft guideline was then submitted for international expert review. The GDG nominated two international experts to review the draft guideline. These reviewers were chosen based on their in-depth knowledge of the subject area and guideline development processes.

3.6 Procedure for updating the National Clinical Guideline

This guideline was published in November 2015 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 review will be subject to the NCEC approval process and noted in the guideline section of the NCCP and NCEC websites.

3.7 Implementation of the National Clinical Guideline

The implementation plan is based on the COM-B theory of behaviour change (Michie et al., 2011), as outlined in the NCCP Methodology Manual 2014. The implementation plan outlines facilitators and barriers to implementation (See Appendix 8 in the full guideline).

A multidisciplinary clinical team is responsible for the implementation of the guideline recommendations. Recommendations have been divided into the key areas of diagnosis, staging, and treatment. All priorities in relation to GTD care are agreed annually by the NCCP and are submitted to the annual HSE Service Plan, which is published on the HSE webpage. The NCCP Cancer Guidelines will be included in the annual service planning process.

3.8 Organisational responsibility

This National Clinical Guideline should be reviewed by the multidisciplinary clinical team and senior management in the hospital to plan the implementation of 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 clinical staff with responsibility for the care of patients with GTD are expected to:

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

3.9 Audit criteria

It is important that both the implementation of the guideline and patient outcomes are audited to ensure that this guideline positively impacts on patient care.

The management of trophoblastic disease in Ireland has been inconsistent due to a deficiency in expertise required to adequately monitor and treat patients with the disease. A National GTD Registry, Monitoring and Advisory Centre is currently being established in Cork University Maternity Hospital to register and audit all referrals.

Outcomes of incidence, efficiency of hCG monitoring and treatment outcomes in those requiring chemotherapy will form major components of national audit and allow international collaboration with other GTD registries worldwide both in terms of audit and future research.

4 Appendices

Appendix 1: NCCP Guideline Development Group membership

Terms of reference

To develop a national evidence-based clinical guideline for the diagnosis, staging and treatment of patients with GTD. Full terms of reference are available in the NCCP Methodology Manual for guideline development.

Membership of the Guideline Development Group

Chair

Ms. Noreen Gleeson Consultant Gynaecological Oncologist, SJH &
The Coombe Women's Hospital

Members

Mr. John Coulter Consultant Obstetrician/Gynaecologist, CUMH
Dr. Dearbhaile O'Donnell Consultant Oncologist, SJH
Dr. Paula Calvert Consultant Medical Oncologist, WRH
Prof. Seamus O'Reilly Consultant Medical Oncologist, CUMH (until Jan 2015)
Ms. Catherine Duffy Co-Project Manager, GTD Tumour Group, NCCP
Ms. Ruth Ryan Co-Project Manager, GTD Tumour Group, NCCP
Dr. Eve O'Toole Guideline Methodologist, NCCP
Mr. Brendan Leen Regional Librarian, HSE South East

Conflict of interest

Members declared no conflicts of interest.

Additional contributors:

NCCP Research Staff

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Acknowledgments

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Dr. Mary Hynes	Deputy Director, NCCP
Dr. Susan O'Reilly	Director, NCCP (until Nov 2014)
Prof. Mike Clarke	Director of MRC Methodology Hub, QUB
Mr. Robin Harbour	Lead Methodologist, SIGN

Charing Cross Hospital
Royal College of Obstetricians and Gynaecologists (RCOG)
European Society for Medical Oncology (ESMO)

Appendix 2: NCCP Guideline Steering Group membership

Terms of reference

To set strategic direction regarding the development of multidisciplinary/interdisciplinary evidence-based clinical practice guidelines for the diagnosis, staging and treatment of cancer. Full terms of reference are available in the NCCP Guideline Methodology Manual for guideline development.

Membership of the NCCP Guideline Steering Group

The NCCP Guideline Steering Group provided governance for the development of the guideline. The members of the steering group are listed below. The GDG project managers were also present at meetings as observers.

Chair

Dr. Jerome Coffey	National Director, NCCP
Dr. Susan O'Reilly	National Director, NCCP (until Nov 2014)

Members

Mr. Justin Geoghegan	Chair Hepatobiliary GI GDG, SVUH
Ms. Noreen Gleeson	Chair Gynaecological GDG, SJH & The Coombe Women's Hospital
Dr. Mary Hynes	Deputy Director, NCCP
Prof. Arnold Hill	NCCP Surgical Oncology Advisor
Dr. Maccon Keane	NCCP Medical Oncology Advisor
Dr. Marcus Kennedy	Chair Lung GDG, CUH
Mr. Brendan Leen	Regional Librarian HSE South-East
Ms. Debbie McNamara	Chair Lower GI GDG, BH
Dr. Deirdre Murray	Health Intelligence, NCCP
Dr. Ann O'Doherty	Chair Breast GDG, SVUH
Dr. Margaret O'Riordan	Medical Director, ICGP (to May 2014)
Dr. Eve O'Toole	Guideline Methodologist, NCCP
Mr. David Quinlan	Chair Prostate GDG, SVUH
Prof. John Reynolds	Chair Gastrointestinal GDG, SJH
Dr. Karen Ryan	Consultant in Palliative Medicine & Clinical Lead Clinical Programme for Palliative Care, SFH

Patients: The views and preferences of the target population were sought by inviting patient advocacy groups to engage in the national stakeholder review process (NCCP Methodology Manual 2014) and also in the development of information materials.

Management: A Cancer Network Manager from the NCCP meets with each cancer centre (CEO/General Manager) on a quarterly basis for performance monitoring and service planning. A lead clinician for Gynaecology Oncology is nominated in each cancer centre.

Appendix 3: Glossary of terms and abbreviations

Definitions within the context of this document

Case control study	The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups. (CEBM website)
Case series	A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. (NCI Dictionary)
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)
External validity	The extent to which we can generalise the results of a study to the population of interest.
Internal validity	The extent to which a study properly measures what it is meant to measure.
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 tumor	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
BH	Beaumont Hospital
CC	Choriocarcinoma
CEBM	Centre for Evidence-Based Medicine
CEO	Chief Executive Officer
CHAMOCA	Cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan and vincristine
CHM	Complete Hydatidiform Mole
CNS	Central Nervous System
CO	Cyclophosphamide and vincristine
COM-B	Capability, Opportunity and Motivation Behaviour Model
CSF	Cerebral Spinal Fluid
CT	Computed tomography
CUMH	Cork University Maternity Hospital
CXR	Chest X-ray
DoHC	Department of Health and Children
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
GP	General Practitioner
GTD	Gestational Trophoblastic Disease
GTN	Gestational Trophoblastic Neoplasia
GUH	Galway University Hospital
hCG	Human Chorionic Gonadotropin
HIPE	Hospital In-Patient Enquiry
HIQA	Health Information and Quality Authority
HM	Hydatidiform Mole
HSE	Health Service Executive
ICGP	Irish College of General Practitioners
IM	Intramuscular
IT	Intrathecal
IV	Intravenous
KCl	Potassium chloride
MAC	Methotrexate, actinomycin D, cyclophosphamide or chlorambucil
MDT	MultiDisciplinary Team
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NCCP	National Cancer Control Programme
NCEC	National Clinical Effectiveness Committee
NETDC	New England Trophoblastic Disease Centre
NMH	National Maternity Hospital
OS	Overall Survival
PET	Positron Emission Tomography

PHM	Partial hydatidiform mole
po	per oratum
PSTT	Placental site trophoblastic tumour
QUB	Queen's University Belfast
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
SFH	St. Francis Hospice
SIGN	Scottish Intercollegiate Guidelines Network
SJH	St. James's Hospital
SVUH	St. Vincent's University Hospital
TE/TP	Paclitaxel/cisplatin and paclitaxel/etoposide
TVU	Transvaginal ultrasound
ULH	University of Limerick Hospitals
WHO	World Health Organisation
WRH	Waterford Regional Hospital



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