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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Cheng H, Zong L, Kong Y, et al. Camrelizumab plus apatinib in patients with high-risk chemorefractory or relapsed gestational trophoblastic neoplasia (CAP 01): a single-arm, open-label, phase 2 trial. *Lancet Oncol* 2021; published online Oct 5. http://dx.doi.org/10.1016/S1470-2045(21)00460-5.

Supplementary Table S1: Details of chemotherapy regimens (cycles) before enrolment and after discontinuation of camrelizumab and apatinib

	Prior chemotherapy regimens at each line before enrolment					Chemotherapy regimens at each line after discontinuation of camrelizumab and apatinib		
	1	2	3	4	5	1	2	3
Patient 1	FAV (9)	EMA/CO (8)	FAEV (6)	EMA/EP (6)	TP (2)			
Patient 2	EMA/CO (5)	EMA/EP (2)	TIP (3)	TE/TP (2)	FAEV (2)			
Patient 3	EMA/CO (3)	FAEV (5)	EMA/CO (11)			EMA/EP (3)		
Patient 4	EMA/CO (3)	EMA/EP (2)	FAEV (1) TIP (1) TE/TP (2)			FAEV (2)		
Patient 5	FAEV (4)	PEB (2)	EMA/EP (7)					
Patient 6	TCF (6)	EMA/CO (1) FAEV (3)	VMP (2)	EP (4)	TC (5)	FAEV (4)		
Patient 7	EMA/CO (9)	FAV (3)						
Patient 8	FA (8)	EMA/CO (7)						
Patient 9	FAEV (4)	EMA/CO (5)	TE/TP (2)			EMA/CO (4) IT MTX (9)		
Patient 10	IM MTX (2)	FA (3)	EMA/CO (9)			FAEV (4)		
Patient 11	IM MTX (4)	Induction EP (6)	EMA/CO (6)	FAEV (2)		FAEV (6)		
Patient 12	FAEV (7)	EMA/CO (4)						
Patient 13	Induction EP (3)	EMA/CO (7)	TE/TP (2)	FAEV (2)		EMA/CO (4)	FAEV (3)	BEP (6)
Patient 14	EMA/CO (7)	FAEV (4)						
Patient 15	IM MTX (4)	FAEV (3)	EMA/CO (3)			EMA/EP (5)	FAEV (2) TE/TP (1)	
Patient 16	FA (10)	EMA/CO (4)						
Patient 17	EMA/CO (8)	FAEV (3)						

Patient 18	IM MTX (9)	EMA/CO (5)	FAEV (5)			EMA/EP (9)		
Patient 19	FAV (4)	FAEV (4)	EMA/CO (5)	FAEV (5)				
Patient 20	Induction EP (4)	EMA/CO (1)	TP (1) FAEV (2)			FAEV (6)		

EMA/CO=etoposide, methotrexate, actinomycin D/cyclophosphamide, vincristine. EMA/EP=etoposide, methotrexate, actinomycin-D/etoposide, cisplatin. EP=etoposide, cisplatin. FA=floxuridine, actinomycin-D. FAEV=floxuridine, actinomycin-D, etoposide, vincristine. FAV=floxuridine, actinomycin-D, vincristine. IM=intramuscular. IT=intrathecal. MTX=methotrexate. PEB=cisplatin, etoposide, bleomycin. TC=paclitaxel, carboplatin. TCF=paclitaxel, cisplatin, floxuridine. TE/TP=paclitaxel, etoposide/paclitaxel, cisplatin. TIP=paclitaxel, ifosfamide, cisplatin. VMP=vincristine, methotrexate, cisplatin. TP=paclitaxel, cisplatin.

Supplementary Table S2: Changes in size of lesions by imaging examinations and serum hCG level for the only patient with placental site trophoblastic tumour

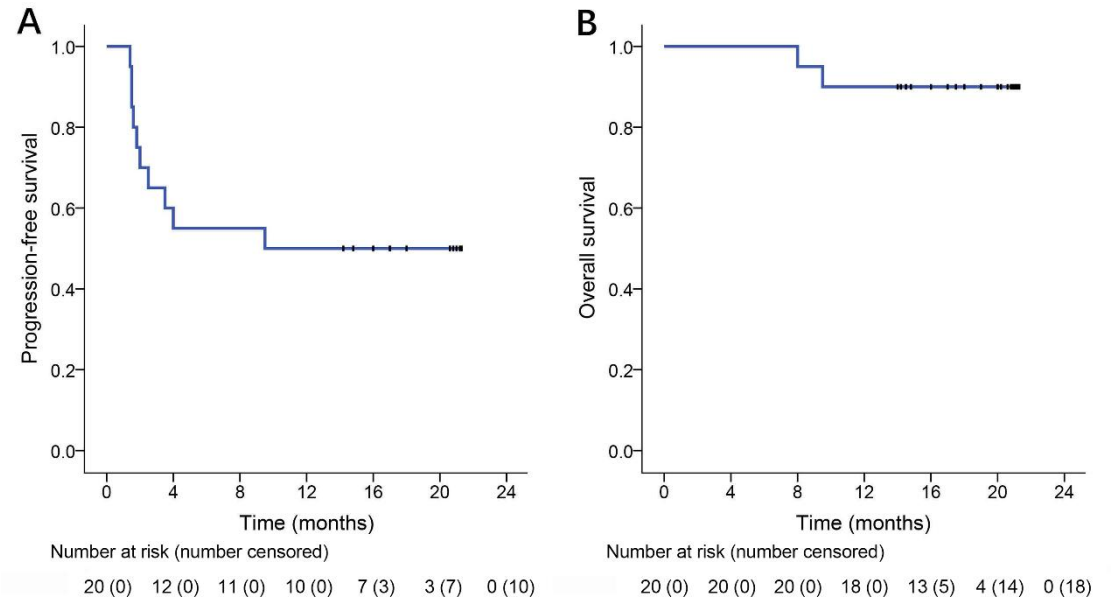
Time point	Size of lesions	Serum hCG level
At enrolment (August 1, 2019)	3·7 cm × 2·9 cm; 3·4 cm × 2·5 cm	492.92 IU/L
Assessed as partial response according to serum hCG level (October 8, 2019)	4·5 cm × 4·2 cm; 3·4 cm × 3·0 cm	85.18 IU/L

hCG=human chorionic gonadotrophin.

Supplementary Table S3: Immune-related adverse events (n=20)

	All grades	Grade 1 or 2	Grade 3
Rash	5 (25)	2 (10)	3 (15)
Reactive cutaneous capillary endothelial proliferation	5 (25)	5 (25)	0
Fever	4 (20)	4 (20)	0
Hyperthyroidism	4 (20)	4 (20)	0
Neutropenia	3 (15)	1 (5)	2 (10)
Lymphopenia	2 (10)	2 (10)	0
Fatigue	2 (10)	2 (10)	0
Hypothyroidism	2 (10)	2 (10)	0
Pruritus	1 (5)	1 (5)	0

Data are n (%). Patients could report more than one adverse event. No grade 4 or 5 immune-related adverse events occurred.



Supplementary Figure S1: Progression-free survival (A) and overall survival (B) of all patients (n=20)

Camrelizumab plus apatinib in patients with high-risk chemo-refractory or relapsed gestational trophoblastic neoplasia: a single-arm, open-label, phase 2 trial

Principal investigator: Prof. Yang Xiang, M.D.

National Clinical Research Centre for Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

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1. Introduction

Gestational trophoblastic neoplasia (GTN) develops from the abnormal proliferation of placental trophoblastic cells and includes malignant invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT), and epithelioid trophoblastic tumour (ETT) (1). The International Federation of Gynecology and Obstetrics (FIGO) 2000 risk scoring system divides GTN patients into a low-risk group (FIGO score <7) and a high-risk group (FIGO score ≥7) (2). Low-risk GTN patients are usually treated with single-agent chemotherapy, and multi-agent chemotherapy regimens are used to treat high-risk GTN (1). Although approximately 100% of low-risk patients, and more than 90% of high-risk patients, can achieve complete response through standard chemotherapy, about 5% of high-risk patients develop chemo-refractory disease or have multiple relapses and die of disease progression (3-5). Brain and/or liver metastases (6, 7), multiple agent chemotherapy-resistant tumours (8), and infrequent pathological types (PSTT and ETT) (9, 10) are adverse features that predict poorer outcomes. Most commonly used salvage therapies for these patients include EMA/EP (etoposide, methotrexate and actinomycin-D/etoposide, cisplatin), FAEV (floxuridine, actinomycin-D, etoposide, vincristine), and TE/TP (paclitaxel, cisplatin/paclitaxel, etoposide) (1). These regimens have shown a 50–75% response rate, with significant grade 3 or 4 toxicities recorded for neutropenia and thrombocytopenia (11-13). However, long-term follow-up revealed that the live birth rate for patients receiving these chemotherapies was approximately 72–76%, and 40% of patients failed to resume normal menstrual function (13-15). Novel approaches for high-risk chemo-refractory or relapsed GTN are urgently needed, particularly for those patients who have experienced failure with multiple chemotherapeutics.

Immunotherapy has been reported as effective in multidrug-resistant high-risk GTN patients (16). Due to the origin of GTN and the constitutional expression of PD-L1 in tumour cells, the reported response rate of PD-1/PD-L1 inhibitors in GTN is higher than that in other solid tumours (16-18). Molecularly targeted agents against the vascular endothelial growth factor (VEGF) have been validated in various advanced tumours (19, 20). High expression of VEGF has also been found in choriocarcinoma and PSTT (21, 22). VEGF regulates the proliferation, differentiation, and invasion of trophoblastic cells (23). Treatment of animal models with antagonists of the VEGF receptor significantly reduces tumour development and progression of choriocarcinoma (24).

Camrelizumab is a fully humanised, high-affinity, monoclonal antibody that binds to PD-1. The clinical efficacy and favourable safety of camrelizumab have been demonstrated in several tumours (25, 26). Apatinib is an oral, small-molecule, tyrosine kinase inhibitor that selectively binds to VEGF receptor 2. It is reported that simultaneous blockade of the VEGF and PD-1/PD-L1 pathways induces a synergistic antitumour effect in vivo, as well as diminishing the risk of immune-related adverse events (27, 28). In this single-arm, open-label, phase 2 trial, we aimed to assess the safety and efficacy of camrelizumab and apatinib as combination therapy in patients with high-risk chemo-refractory or relapsed GTN.

2. Objectives

2.1 Primary objective

The primary endpoint is objective response rate, defined as the proportion of patients with complete or partial response according to the serum human chorionic gonadotrophin (hCG) level.

2.2 Secondary objectives

Progression-free survival

- The time from the treatment initiation to disease progression according the serum hCG level or death, whichever came first.

Duration of response

- The time from the first evidence of response to disease progression or death, whichever came first.

Overall survival

- The time from the treatment initiation to the date of death or end of follow-up

Safety as measured by adverse events

- National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 is used to evaluate the grade of adverse events, to observe any adverse event and serious adverse event that occurred in all patients during the clinical study period, including abnormal laboratory examination results, clinical manifestations and vital signs, to record their clinical manifestation characteristics, severity, occurrence time, duration, corresponding treatment and prognosis, and to determine their relationship with the study drug.

3. Study design and sample size

3·1 Study design

This study is a single-arm, open label, phase 2 trial conducted at Peking Union Medical College Hospital.

3·2 Sample size

Based on early data in our center, the objective response rate of the combination regimen (camrelizumab plus apatinib) for high-risk chemo-refractory or relapsed GTN was estimated to reach 50% in this study. The Clopper-Pearson method was used to calculate the corresponding 95% CI of objective response rate. The trial was designed to enrol 18 evaluable patients to provide an objective response rate of 50% with a 95% CI half-width of 24% (26%–74%). Considering a 10% dropout rate, a

total of 20 patients should be enrolled in this study.

4. Patients

4·1 Inclusion criteria

- Woman aged 18–70 years;
- Patients with high-risk chemo-refractory or relapsed GTN
- Patients who have previously received two or more lines of combination chemotherapies;
- Patients with a prognostic score ≥7 according to the International Federation of Gynecology and Obstetrics (FIGO) 2000 staging and risk factor scoring system;
- Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2;
- Patients with abnormal serum hCG level (≥5 IU/L);
- Expected survival ≥ 4 months;
- The function of vital organs meets the following requirements:

  hemoglobin ≥80 g/L, absolute neutrophil count ≥1·5×10^9/L, platelets ≥100×10^9/L;

  creatinine ≤1·5 × upper limit of normal (ULN), urea nitrogen ≤2·5×ULN;

  total bilirubin ≤ULN, alanine aminotransferase and aspartate aminotransferase ≤2·5×ULN, albumin ≥25 g/L;

  thyroid stimulating hormone ≤ULN (if thyroid stimulating hormone is abnormal, normal T3 and T4 can also be acceptable).
- Female patients of childbearing age must exclude pregnancy and are willing to use a medically approved high-efficiency contraceptive (e.g., intrauterine device, contraceptive or condom) during the study period and within 3 months of the last study drug administration.
- The patient should be aware of the purpose of the study and the operations required by the study and volunteer to participate in the study before sign the informed consent form.

4·2 Exclusion criteria

- Previous treatment with immunotherapy drugs (including antibodies targeting PD-1, PD-L1, cytotoxic T-lymphocyte-associated protein 4, T-cell receptor, chimeric antigen receptor T-cell therapy, and other immunotherapy), anti-angiogenic small-molecule tyrosine kinase inhibitors (such as pazopanib, sorafenib, or regorafenib), or anti-angiogenic monoclonal antibodies (such as

bevacizumab); live vaccines injected within 4 weeks before the first dose of study drug; other clinical trials of antitumour drugs within 4 weeks before the first dose of study drug;

- Other malignancies in the past 3 years;
- Immunosuppressive drugs used within 14 days prior to the first dose of camrelizumab; any active autoimmune disease or a history of autoimmune disease;
- Uncontrollable hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, despite with the optimal drug therapy);
- Grade II or higher myocardial ischemia, myocardial infarction or poorly controlled arrhythmia (females with QTc interval ≥470 ms); grade III to IV cardiac insufficiency according to New York Heart Association (NYHA) criteria, or cardiac color Doppler ultrasound evidence of left ventricular ejection fraction <50%; myocardial infarction, NYHA grade II or above heart failure, uncontrolled angina, uncontrolled severe ventricular arrhythmia, clinically significant pericardial disease, or electrocardiogram suggesting acute ischemia or abnormal active conduction system occurring within 6 months before enrolment,
- Abnormal coagulation (international normalised ratio >1·5×ULN or prothrombin time >ULN+4 seconds or activated partial thromboplastin time >1·5×ULN), with bleeding tendency or undergoing thrombolysis or anticoagulant therapy;
- Severe infections within 4 weeks prior to the first dose of study drug (e.g., need of intravenous infusion of antibiotics, antifungal or antiviral drugs), or unexplained fever (>38·5°C) during screening or the first dose of study drug;
- With a history of psychotropic drug abuse and are unable to withdraw the psychotropic drug, or have mental disorders;
- Major surgery performed within 4 weeks before the first dose of study drug, or open wounds or fractures;
- Obvious factors affecting oral drug absorption, such as inability to swallow, chronic diarrhea and intestinal obstruction, or sinus or perforation of empty organs within 6 months
- Routine urine test indicating urinary protein ++ or more, or confirmed urinary protein ≥1·0 g within 24 hours;
- Human immunodeficiency virus infection or known acquired immunodeficiency syndrome, active

hepatitis B (HBV DNA (>500 IU/mL), hepatitis C (hepatitis C antibody positive, and HCV-RNA higher than the lower limit of the analysis method) or co-infection with hepatitis B and hepatitis C.

- Other reasons as judged by the investigator

5. Treatment and administration

- Camrelizumab 200 mg intravenously once every 2 weeks
- Apatinib 250 mg orally once per day

Four weeks are deemed as a cycle. Treatment will be continued until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will receive 6 cycles of consolidation therapy if achieving a complete response.

6. Dose modification

Dose modification of camrelizumab is not permitted. Dose reductions and interruptions of apatinib are permitted if toxicities that are not relieved by supportive care.

6·1 Dose interruptions

The interruption of apatinib within 4 weeks is acceptable. If the toxicity cannot be relieved to grade ≤1 after 4 weeks' interruption, apatinib will be discontinued permanently.

6·2 Dose reductions

The first dose reduction of apatinib is to 250 mg once per day with 2 days on and 1 day off, and additional reduction is to 250 mg once per day every other day. If the apatinib dose is reduced, it cannot be increased.

7. Study procedures

7·1 Screening phase

Screening procedures will be completed within 14 days before treatment:

- Review of eligibility criteria
- Signed informed consent

- Review of medical history and demographics
- Physical examinations
- Vital signs
- ECOG performance status
- Serum hCG level
- laboratory tests including hematological, biochemical, endocrinologic, virological, and urine/faces examinations;
- Electrocardiogram/echocardiography;
- Thoracic contrast-enhanced computed tomography (CT) scan, and abdominal-pelvic and brain contrast-enhanced CT or magnetic resonance imaging (MRI) scans;

7·2 Treatment phase

During camrelizumab plus apatinib treatment, serum hCG levels will be measured weekly. For patients achieving a complete response, serum hCG level will be measured every 2 weeks to 6 months, every month to 1 year, every 3 months to 2 years, every 6 months to 3 years, and annually thereafter. Blood routine and hepatic/renal function examinations will be done every 2 weeks. The other haematological, biochemical, endocrinological, and urine and faeces examinations will be done every cycle. Electrocardiogram or echocardiography will be done every 2 cycles. Urinary protein quantity in 24 hours will be tested if urinary protein is 2+.

CT or MRI will be performed every 2 cycles for patients with measurable lesions at baseline. For patients without measurable lesions at baseline, radiographic assessments will be performed when necessary, as judged by the investigator.

Adverse events will be monitored throughout the treatment period based on patient report, investigator observation, and each examination.

7·3 Post-treatment phase

Treatment will be continued until disease progression, or unacceptable toxicity, or withdrawal of consent. Patients will receive 6 cycles of consolidation therapy if achieving a complete response.

Once the patient discontinues the treatment, drug-related adverse events during treatment or until 30 days (90 days for serious adverse events) after the last dose of study drug should be recorded.

8. Efficacy

Response will be assessed by the investigator every 2 cycles based on the serum hCG level.

- Complete response is defined as normal serum hCG level measured for 3 consecutive weeks.
- Partial response is defined as ≥50% decrease in hCG level from baseline after 2 cycles.
- Stable disease is defined as <50% decrease in hCG level from baseline after 2 cycles.
- Progressive disease is defined as any increase in serum hCG level from baseline after 2 cycles or the presence of new metastatic lesions.

8·1 Primary endpoint

The primary endpoint is objective response rate, defined as the proportion of patients with complete or partial response according to the serum hCG level.

8·2 Secondary endpoints

Progression-free survival is defined as the time from the treatment initiation to disease progression according the serum hCG level or death, whichever came first.

Duration of response is defined as the time from the first evidence of response to disease progression or death, whichever came first.

Overall survival is defined as the time from the treatment initiation to the date of death or end of follow-up.

Safety is measured by the frequency of adverse events that occur in the treatment.

9. Safety evaluation

9·1 Adverse event

An adverse event is any adverse medical occurrence after a patient administered a medical drug. An adverse event does not necessarily have a causal relationship with the treatment. Any adverse symptom or sign, laboratory abnormality, or illnesses that occur from the time patients sign the informed consent until 30 days after the last dose of the study drug should be collected. adverse events include the following:

- Exacerbation of the existing medical condition/disease (including symptoms, signs, and laboratory tests) prior to entering the clinical trial;
- Any newly occurring adverse medical conditions (including symptoms, signs, and newly

diagnosed diseases);

- Abnormal laboratory test values or results of clinical significance;

The investigators should record any adverse event in details, including adverse events and all associated symptoms description, occurrence time, severity, relationship with the study drug, duration, corresponding treatment, and final outcomes.

9·2 Serious adverse event

A serious adverse event is defined as harmful adverse event that occurs at any dose and meets the following criteria:

- Results in death or life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical event that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All serious adverse events occurring during the study must be reported to Institutional Review Board (IRB) within 24 hours. The initial and follow-up reports of a serious adverse event should be made.

9·3 Safety analysis

All patients who have received at least one dose of study drug will be included in the safety analysis. NCI-CTCAE 5.0 is used to evaluate the grade of adverse events, to observe any adverse events and serious adverse events that occurred in all patients during the clinical study period, including abnormal laboratory examination results, clinical manifestations and vital signs, to record their clinical manifestation characteristics, severity, occurrence time, duration, treatment method and prognosis, and to determine their relationship with the study drug.

10. Statistical analysis

10·1 Study population definitions

In this study the following three populations will be defined for the analysis.

- Full analysis set: all patients who receive at least one dose of study drug.
- Per-protocol set: A subset of the patients who meet all the trial criteria and are complaint with the protocol and absence of any major protocol violations.
- Safety set: all patients who receive at least one dose of study drug.

10·2 Efficacy analysis

Objective response rate is defined as the proportion of patients with complete or partial response according to the serum hCG level.

Progression-free survival is defined as the time from the treatment initiation to disease progression according the serum hCG level or death, whichever came first.

Duration of response is defined as the time from the first evidence of response to disease progression or death, whichever came first.

Overall survival is defined as the time from the treatment initiation to the date of death or end of follow-up.

10·3 Safety analysis

All adverse events, deaths, clinical laboratory results and vital sign measurements will be included in the safety analysis.

10·4 Analysis methods

Patients' baseline characteristics will be summarised for the full analysis set. The efficacy analysis will be performed on both the full analysis set and per-protocol set. Safety analysis will be performed on the safety set.

Efficacy analysis: The objective response rate will be evaluated by the number and proportion of patients with complete or partial response. The Clopper-Pearson method will be used to calculate the corresponding 95% CI of objective response rate. Duration of response, progression-free survival, and overall survival will be assessed by Kaplan-Meier method.

Safety analysis: The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, and clinical laboratory results.

All analyses will be performed using SPSS 22.0.

11. Regulatory ethics compliance

11·1 Investigator responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guideline on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

11·2 Informed consent

Each patient must give written consent according to local requirements after the nature of the study has been fully explained. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements.

Before enrolment in the study, the investigator must explain to potential patients the aims, methods, reasonably anticipated benefits, and potential hazards of the study, any discomfort participation in the study may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the patient will receive for the treatment. The patient will be given the opportunity to ask questions. After the explanation and before entry into the study, consent should be recorded by the patient's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the patient.

11·3 Compensation to research patients

A patient is entitled to compensation if injury or death is due to adverse effect of investigational products. Compensation must be consistent with the laws, regulations, and guidelines of the region in which the study is conducted.

11·4 Institutional review board

Before the start of the study, the investigator will provide the IRB with current and complete copies of the documents, which include, but are not limited to, final protocol, informed consent, investigators' curriculum vitae, information regarding funding, and other potential conflicts of interest. The study will be undertaken only after the IRB has given full approval of all the documents. All the protocol amendments must be submitted to the IRB for review and approval before implementation of the changes.

12. Administrative requirements

The investigators should perform the following aspects, which include, but are not limited to, protocol amendments, regulatory documentation, case report form completion, record retention, monitoring, and data quality control.

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