

**A.L. 490 ta' l-2004****ATT TA' L-2003 DWAR IL-MEDIĊINI  
(ATT NRU. III TA' L-2003)****Regolamenti ta' l-2004 Dwar Provi Kliniċi**

BIS-SAHHA tas-setgħat mogħtija bl-artikolu 106 ta' l-Att ta' l-2003 dwar il-Mediċini, il-Ministru tas-Sahha, Anzjani u Kura fil-Komunità għamel dawn ir-regolamenti li ġejjin:

**1.** It-titolu ta' dawn ir-regolamenti hu Regolamenti ta' l-2004 Titolu.  
dwar Provi Kliniċi.

**2.** (1) Dawn ir-regolamenti qegħdin jimplementaw id-Direttiva Għan.  
2001/20/KE u ser jirregolaw it-tmexxija ta' provi kliniċi, inklużi provi  
li jsiru f'ħafna ċentri, f'Malta fuq suġġetti umani u li jinvolvu prodotti  
medicinali kif definiti fl-Att, u partikolarment f'dak li għandu x'jaqsam  
ma' l-implimentazzjoni ta' Prattika klinika tajba. Dawn ir-regolamenti  
ma japplikawx għal provi li ma jinvolvux intervent.

(2) Kull prova klinika inklużi studji fuq biodisponibilità u  
bioekwivalenza għandha tkun iddisinjata, immexxija u rappurtata skond  
il-prinċipji ta' Prattika klinika tajba. L-aspetti varji li huma assoċjati  
ma' sottomissjonijiet inklużi notifikazzjonijiet u talbiet lill-Awtorità  
dwar il-Liċenzi u lill-Kumitat ta' L-Etika u l-proċeduri u l-  
kundizzjonijiet l-oħra kollha relatati ma' provi kliniċi kif meqjusa bhala  
neċessarji mill-Awtorità dwar il-Liċenzi, għandhom ikunu skond il-  
pubblikazzjonijiet relatati ma' provi kliniċi li huma pubblikati u, jew  
adottati perjodikament mill-Kummissjoni kif meqjusin neċessarji mill-  
Awtorità dwar il-Liċenzi.

**3.** F'dawn ir-regolamenti kemm-il darba r-rabta tal-kliem ma Tifsiriet.  
tkunx teħtieġ xort' oħra.

“Aġenzija” tfisser l-Aġenzija Ewropea dwar Mediċini  
stabbilita bir-regolament (EC) Nru 726/2004;

“*brochure* ta' l-investigatur” tfisser kumpilazzjoni tat-tagħrif  
kliniku u mhux kliniku dwar prodott jew prodotti medicinali  
investigattivi li huma rilevanti għall-istudju tal-prodott jew prodotti  
f'suġġetti umani;

“grajja kuntrarja” tfisser kull grajja medika mhux mistennija f’pazjent jew suġġett ta’ prova klinika li lili jiġi amministrat prodott mediċinali u li mhux neċessarjament ikollha relazzjoni kawżali ma’ din il-kura;

“grajja kuntrarja serja” jew “reazzjoni kuntrarja serja” tfisser kull grajja medika mhux mistennija jew effett mhux mistenni fejn kull doża twassal għall-mewt, ikun ta’ theddida għall-hajja, jehtieg dhul fi sptar jew itawwal iż-żmien ta’ dewmien fi sptar, jirriżulta f’ diżabilità jew inkapaċità persistenti jew sinifikanti, jew ikun anomalija kongenitali jew difett mit-twelid;

“investigatur” tfisser tabib jew persuna li tkun kwalifikata kif imiss u approvat mill-Awtorità dwar il-Liċenzi biex taghmel investigazzjonijiet minhabba fl-isfond xjentifiku u l-esperjenza fil-kura ta’ l-pazjenti li tali investigazzjoni tkun tehtieg. L-investigatur ikun responsabbli għat-tmexxija tal-prova klinika f’sit ta’ prova. Jekk prova titmexxa minn *team* ta’ individwi f’sit ta’ prova, l-investigatur ikun il-persuna responsabbli għat-*team* u dan jista’ jissejjah l-investigatur prinċipali;

“kumitat ta’ l-etika” tfisser korp indipendenti, magħmul minn professjonisti fil-kura tas-saħha u membri mhux mediċi, li r-responsabbiltà tagħhom hija li jharsu d-drittijiet, is-sigurtà u l-benesseri ta’ suġġetti umani involuti fi prova u li jipprovdu assikurazzjoni pubblika għal dak il-harsien, billi, fost hwejjeġ ohra, jesprimu opinjoni dwar il-protokoll ta’ prova, l-idoneità ta’ l-investigaturi u l-adegwatezza tal-faċilitajiet, u dwar il-metodi u d-dokumenti li għandhom jintużaw biex suġġetti taht prova ikunu reklutati u nformati u biex jinkiseb il-kunsens informat tagħhom;

“kunsens infurmat” tfisser deċiżjoni, li għandha tkun miktuba, f’wahda mill-lingwi uffiċjali ta’ Malta jew fi lsien li s-suġġett ta’ prova klinika u, jew ir-rappreżentant legali tiegħu ikunu jifhmu, kif ukoll datata u ffirmata, biex is-suġġett jiehu sehem fi prova klinika, li ssir liberament wara li s-suġġett jiġi informat kif imiss dwar in-natura, sinifikat, implikazzjonijiet u riskji tagħha, u dan ikun dokumentat kif imiss, minn kull persuna li kapaci taghti l-kunsens jew, fejn il-persuna ma tkunx kapaci li taghti l-kunsens, mir-rappreżentant legali tiegħu jew tagħha; jekk dik il-persuna ma tkunx taf tikteb, jista’ jinghata kunsens bil-fomm fil-presenza ta’ għallinqas xhud wiehed.

“prattika tajba ta’ klinika” tfisser sett ta’ htigiet ta’ kwalità etika u xjentifika b’ għarfien internazzjonali li għandhom jiġu osservati biex jiġu disinjati, mwettqa, reġistrati u rapportati provi

kliniċi li jinvolvu l-partecipazzjoni ta' suġġetti umani. Konformità ma' din il-prattika tajba tagħti assikurazzjoni li jhassru d-drittijiet, is-sigurtà u l-benesseri tas-suġġetti taht prova u li r-rizultati tal-provi kliniċi huma kredibbli;

“prodott mediċinali investigattivi”: tfisser forma farmaċewtika ta' sustanza attiva jew *placebo* li jkunu qed jiġu ttestjati jew użat bhala referenza fil-prova klinika, inklużi prodotti li ġa jkollhom l-awtorizzazzjoni tat-tqeghid fis-suq iżda wżati jew miġbura (formulati jew pakkettjati) b' mod differenti mill-forma awtorizzata, jew meta wżati għal indikazzjoni mhux awtorizzata, jew meta wżati biex jinkiseb aktar tagħrif dwar il-forma awtorizzata;

“protokoll” tfisser dokument li jiddeskrivi l-ghan jew ghanijiet, disinn, metodoloġija, konsiderazzjonijiet statistiċi u l-organizzazzjoni ta' prova. L-espressjoni protokoll tirreferi għall-protokoll, verżjonijiet suċċessivi tal-protokoll u emendi li jsiru fil-protokoll;

“prova klinika” tfisser kull investigazzjoni f' suġġetti umani maħsuba biex tiskopri jew tivverifika l-effetti kliniċi, farmakoloġiċi u, jew farmakodinamiċi ohra ta' xi prodott mediċinali investigattiv u, jew tidentifika kull reazzjoni kuntrarja għal xi prodott mediċinali investigattiv u, jew tistudja l-assorbiment, tqassim, metabolizmu u eliminazzjoni ta' xi prodott mediċinali nvestigattiv bil-ghan li tiġi żgurata s-sigurtà u, jew l-effikaċja tiegħu. Dan jinkludi provi kliniċi mwettqa jew f'xi wiehed jew f'diversi siti, sew fi Stat Membru wiehed jew aktar;

“prova mhux ta' intervent” tfisser studju fejn prodott mediċinali jiġi preskritti bil-mod normali skond il-pattijiet ta' l-awtorizzazzjoni tat-tqeghid fis-suq. In-nomina ta' pazjent għal strateġija partikolari ta' terapija ma tiġix deċiża bil-quddiem minn protokoll ta' prova iżda taqa' fi hdan il-prattika kurrenti u l-preskrizzjoni tal-mediċina hija separata b' mod ċar mid-deċiżjoni biex il-pazjent jiġi inkluż fl-istudju. Ebda dijanjosi addizzjonali jew proċeduri ta' monitoraġġ ma għandhom jiġu applikati lill-pazjenti u għandhom jintużaw metodi epidemjoloġiċi għall-analiżi tat-tagħrif miġbur;

“prova klinika f'ħafna ċentri” tfisser prova klinika li tkun tmexxiet skond protokoll uniku iżda f'aktar minn sit wiehed, u għalhekk minn aktar minn investigatur wiehed, li fih is-siti ta' prova jistgħu jinsabu fi Stat membru wiehed, f'diversi Stati Membri u, jew fi Stati Membri u pajjiżi terzi;

“reazzjoni kuntrarja” tfisser kull reazzjoni mhux mistennija jew mhux intenzjonata għall-prodott mediċinali ta’ investigazzjoni relatat ma’ xi doża amministrata;

“reazzjoni kuntrarja mhux mistennija” tfisser reazzjoni kuntrarja, li x-xorta jew is-severità tagħha ma tkunx konsistenti mat-tagħrif rilevanti għall-prodott bħal *brochure* ta’ investigatur għal prodott investigattiv mhux awtorizzat jew sommarju ta’ karatteristiċi ta’ prodott għal prodott awtorizzat;

“spezzjoni” tfisser l-att mill-awtorità kompetenti kif t-tmexxa reviżjoni uffiċjali tad-dokumenti, faċilitajiet, *records*, arrangamenti dwar assikurazzjoni ta’ kwalità, u kull riżors ieħor meqjus mill-awtorità kompetenti li jkun relatat mal-prova klinika u li jista’ jiġi lokat fis-sit tal-prova, fil-faċilitajiet ta’ l-isponser u, jew ta’ l-organizzazzjoni ta’ riċerka b’kuntratt, jew fi stabbilimenti oħra li l-awtorità kompetenti tqis li jkun xieraq li tispezzjona;

“sponser” individwu, kumpannija, istituzzjoni jew organizzazzjoni li tiehu responsabbiltà għal bidu, l-immaniġġar u, jew l-iffinanzjar ta’ prova klinika;

“suġġett” individwu li jiehu sehem fi prova klinika jew bhala min jirċievi i-prodott mediċinali investigattiv jew li fuqu jsir kontroll.

Protezzjoni ta’  
suġġetti ta’ prova  
klinika.

#### 4. (1) Prova Klinika tista’ ssir biss jekk partikolarment:

(a) ir-riskji u inkonvenjenzi prevedibbli jkunu twiežnu kontra l-benefiċċju antiċipat għas-suġġett ta’ prova individwali u pazjenti oħra attwali u futuri. Prova klinika tista’ tinbeda biss jekk il-Kumitat ta’ l-Etika u, jew l-Awtorità dwar il-Licenzi jaslu għall-konklużjoni li l-benefiċċji terapewtiċi u ta’ saħħa pubblika antiċipata jkunu jiġġustifikaw ir-riskji u jistgħu jitkomplew biss jekk il-konformità ma’ din il-htieġa tkun permanentement u kontinwament sorveljata;

(b) is-suġġett ta’ prova jew, meta l-persuna ma tkunx tista’ tagħti l-kunsens infurmat tagħha, ir-rappreżentant legali tagħha, kellu l-oportunità, f’intervista li tkun saret qabel ma’ l-investigatur jew ma membru tat-*team* ta’ investigazzjoni, li jifhem l-għanijiet, ir-riskji u l-inkonvenjenzi tal-prova, u l-kondizzjonijiet li taħthom din għandha titmexxa u jkun ġie avżat ukoll bid-dritt li jkollu li jirtira mill-prova f’kull żmien mingħajr ma jsofri dannu;

(c) ikunu tharsu d-drittijiet tas-sugġett għall-integrità fiżika u mentali, għall-privatezza u għall-protezzjoni tad-data dwaru skond l-Att dwar il-Protezzjoni u l-Privatezza tad-Data u kull emenda għaliha;

(d) is-sugġett taht prova jew, meta il-persuna ma tkunx tista' tagħti l-kunsens infurmat, ir-rappreżentant legali tagħha ikun ta l-kunsens tiegħu bil-miktub wara li jkun ġie infurmat bix-xorta, sinifikat, implikazzjonijiet u riskji tal-prova klinika. Iżda jekk l-individwu ma jkunx jaf jikteb, jista' jinghata kunsens bil-fomm fil-presenza għallinqas ta' xhud wiehed;

(e) ikun ġie provdut dwar assigurazzjoni jew indemnità biex tkopri r-responsabbiltà ta' l-investigatur u l-isponser.

(2) Għandha tkun ir-responsabbiltà ta' tabib imsemmi b'ismu, li jkun kwalifikat kif imiss, jew, meta jkun adatt, ta' dentist kwalifikat imsemmi b'ismu jew ta' persuna oħra msemmija b'isimha bi kwalifiki kif imiss skond il-każ, biex f'kull waqt jipprovdi il-kura medika meħtieġa u jiehu d-deċizzjonijiet mediċi għan-nom tas-sugġetti.

(3) Is-sugġett għandu jinghata post ta' riferiment minn fejn ikun jista' jikseb aktar taġrif.

**5.** Mingħajr preġudizzju għal kull restrizzjoni oħra rilevanti, prova klinika fuq minuri għandha titwettaq biss jekk:

Provi kliniċi fuq minuri.

(a) jkun ġie miksub il-kunsens infurmat tal-ġenituri jew rappreżentant legali il-kunsens għandu jkun jirrappreżenta x-xewqa preżunta tal-minuri u jista' jkun revokat f'kull waqt mingħajr ebda detriment għall-minuri;

(b) il-minuri jkun irċieva taġrif skond il-kapaċità tiegħu li jifhem, minn persunal b'esperjenza dwar minuri, dwar il-prova, ir-riskji u l-benefiċċji;

(c) ix-xewqa espliċita ta' minuri li jkun kapaċi jifforma opinjoni u jistma dan it-taġrif li jirrifjuta li jiehu sehem jew li jiġi rtirat mill-prova klinika f'kull waqt, tkun ikkunsidrata mill-investigatur jew, meta jkun adatt, mill-investigatur prinċipali;

(d) ebda inċentiv jew motiv finanzjarju ma għandu jinghata hlief kumpens miftiehem;

(e) ikun mistenni xi benefiċċju dirett għall-grupp ta' pazjenti mill-prova klinika u dan biss meta riċerka bħal dik tkun essenzjali

biex tivvalida data miksuba minn provi kliniċi fuq persuni li ghandhom il-kapaċità li jagħtu l-kunsens infurmat jew b'metodi oħra ta' riċerka; barra minn hekk, dik ir-riċerka għandha jew tkun tirrelata direttament għal kondizzjoni klinika li minnha jkun ibati l-minuri involut jew tkun ta' xorta li tkun tista' titwettag biss fuq il-minuri;

(f) jkunu tharsu l-linji ta' gwida xjentifiċi li jikkorrispondu ta' l-Aġenzija;

(g) ikunu ġew disinjati provi kliniċi biex jitnaqqas l-uġiġh, l-iskumdità, il-biża' jew kull riskju iehor prevedibbli li għandu x'jaqsam mal-marda u l-istadju ta' żvilupp; kemm l-għatba tar-riskju u l-grad ta' tbatija għandhom jiġu speċjalment definiti u sorveljati kontinwament;

(h) il-Kumitat ta' l-Etika, b'kompetenza fil-pedjatrija jew wara li jkun ha l-parir dwar problemi kliniċi, etiċi u psikosoċjali fil-qasam tal-pedjatrija, ikun ikkonferma l-protokoll; u

(i) l-interessi tal-pazjenti dejjem jirbhu fuq dawk tax-xjenza u tas-soċjetà.

Provi kliniċi fuq adulti inkapaċi li jagħtu kunsens legali infurmat .

**6. (1)** Sabiex jsriu provi klinici fuq persuni adulti li ma humiex kapaċi jagħtu kunsens legali infurmat, għandhom japplikaw il-htiġiet kollha relevanti elenkati għall-persuni kapaċi li jagħtu dak il-kunsens. B'żieda ma' dawn il-htiġijiet, il-parteciġazzjoni fi provi kliniċi adulti inkapaċi tali li ma jkunux taw jew ma jkunux irrifjutaw kunsens infurmat qabel ma tkun ġiet fuqhom l-inkapaċità tagħhom, għandha tkun permessa biss jekk:

(a) il-kunsens infurmat tar-rappreżentant legali jkun inkiseb; il-kunsens għandu jkun jirrifletti r-rieda prezunta tas-suġġett u jista' jiġi revokat f'kull żmien, minghajr dannu għas-suġġett;

(b) il-persuna li ma tkunx kapaċi li tagħti kunsens legali infurmat tkun irċeviet tagħrif skond il-kapaċità tagħha li tifhem fir-rigward tal-prova, ir-riskji u l-benefiċċji;

(c) ix-xewqa espliċita tas-suġġett li jkun kapaċi li jiffirma opinjoni u jistma dan it-tagħrif li jirrifjuta li jiehu sehem fi jew li jiġi rtirat mill-prova klinika f'kull waqt, jitqies mill-investigatur jew skond ma jkun adatt mill-investigatur prinċipali;

(d) ma jingħataw ebda inċentiv jew motiv finanzjarju hliet kumpens miftiehem;

(e) riċerka bħal dik hija essenzjali biex jiġi konvalidat it-tagħrif miksub fi provi kliniċi fuq persuni li kapaci jagħtu kunsens infurmat jew b'metodi oħra ta' riċerka u tkun tirrelata direttament ma' xi kondizzjoni klinika li thedded il-hajja jew li tindebbolixxi u l-pazjent inkapaċitat involut ikun ibati biha;

(f) jkunu ġew imfassla provi kliniċi biex ikunu minimizzati l-uġiġh, l-iskumdità, il-biża' u kull riskju iehor prevedibbli b'relazzjoni mal-marda u l-istadju ta' żvilupp; kemm il-livell ta' riskju u kemm il-grad ta' tbatija għandhom ikunu speċjalment definiti u sorveljati kontinwament;

(g) il-Kumitat ta' l-Etika, b'kompetenza fil-marda relevanti u l-popolazzjoni ta' pazjenti involuti jew wara li jieħu parir fi kwistjonijiet kliniċi, etiċi u psikosoċjali fil-qasam tal-marda relevanti u tal-popolazzjoni ta' pazjenti involuti, ikun ikkonferma l-protokoll;

(h) l-interessi tal-pazjent ikunu dejjem jirbhu fuq dawk tax-xjenza u tas-soċjetà; u

(i) ikun hemm raġunijiet biex wiehed jistenna li l-amministrazzjoni tal-prodott mediċinali li għandu jiġi ttestjat johlq benefiċċju għall-pazjent li jkun jeċċedi r-riskji involuti jew li jkun ma johlq ebda riskju.

7. (1) L-Awtorità dwar il-Licenzi għandha twaqqaf Kumitat ta' l-Etika, li għandu jagħti l-opinjoni tiegħu fuq kull kwistjoni rikjest qabel ma jibda xi prova klinika. Kumitat ta' l-Etika.

(2) Fit-thejjija ta' l-opinjoni tiegħu, il-Kumitat ta' l-Etika għandu jikkunsidra, b'mod partikolari:

(a) ir-relevanza tal-prova klinika u l-pjan tal-prova;

(b) jekk il-valutazzjoni tal-benefiċċji mistennija u r-riskji kif meħtieġa skond ir-regolamenti 4 (1) (a) ta' dawn ir-regolamenti tkunx sodisfaċenti u jekk il-konkluzjonijiet ikunux ġustifikati;

(ċ) il-protokoll;

(d) l-idoneità ta' l-investigatur u tal-persunal li jgħinu;

(e) il-*brochure* ta' l-investigatur;

(f) il-kwalità tal-faċilitajiet;

(g) l-adeqwatezza u s-shuhija tat-tagħrif bil-miktub li għandu jingħata u l-proċedura li għandha tiġi segwita bil-għan li jinkiseb kunsens infurmat u l-ġustifikazzjoni għal riċerka fuq persuni li mhux kapaċi jagħtu kunsens infurmat fir-rigward tar-restrizzjonijiet speċifiċi stipulati fir-regolament 4;

(h) dispożizzjoni għall-indennizz jew kumpens fil-każ ta' korriment jew mewt attribwibbli għal prova klinika;

(i) kull assikurazzjoni jew indennizz li jkopru r-responsabbiltà ta' l-investigatur uta' l-isponser;

(j) l-ammonti u, meta jkun adatt, l-arranġamenti dwar il-premjazzjoni ġusta ta' l-investigaturi u l-kumpens li jingħata lis-sugġetti ta' prova u l-aspetti rilevanti ta' kull ftehim bejn l-isponser u s-sit;

(k) l-arranġamenti għar-reklutaġġ tas-sugġetti.

(3) (a) Il-Kumitat ta' l-Etika għandu mhux iżjed tard minn 60 jum mid-data li fiha jirċievi applikazzjoni valida jagħti l-opinjoni motivata tiegħu lill-applikant u lill-Awtorità dwar il-Liċenzi.

(b) Fil-perjodu ta' l-eżami ta' l-applikazzjoni biex tingħata opinjoni, il-Kumitat ta' l-Etika jista' jibgħat talba wahda għal tagħrif supplimentari għal dak għà provdut mill-applikant. Il-perjodu msemmi fil-paragrafu (a) għandu jiġi sospiż sakemm jiġi riċevut it-tagħrif supplimentari.

(4) Ebda estensjoni tal-perjodu ta' 60 jum imsemmi fis-sub regolament (3) ta' dan ir-regolament ma għandha tkun permessa hlief fil-każ ta' provi li jinvolvu prodotti mediċinali għat-terapija tal-ġene jew terapija ta' ċelluli somatiċi jew prodotti mediċinali li jkun fihom organiżmi ġenetikament modifikati. F'dan il-każ, estensjoni sa massimu ta' tletin jum għandha tkun permessa. Għal dawn il-prodotti, dan il-perjodu ta' 90 jum jista' jittawwal b'90 jum oħra fil-każ ta' konsultazzjoni ta' xi grupp jew kumitat. Fil-każ ta' terapija ta' ċelluli żenogeniċi, ma għandu jkun hemm ebda termini ta' żmien mal-perjodu ta' awtorizzazzjoni.

Opinjoni  
wahdanija.

**8.** (1) Fil-każ ta' provi kliniċi f'hafna ċentri limitat għat territorju ta' Malta għandu jkun hemm biss fil-konfront ta' dawk il-provi opinjoni unika mill-Kumitat ta' l-Etika.

(2) Fil-każ ta' provi klinici f'hafna centri, li jkunu qed isiru fl-istess hin f'aktar minn Stat Membru wiehed, ghandha tinghata opinjoni unika mill-Kumtat ta' l-Etika ghall-kull Stat Membru involut bil-prova klinika.

9. (1) Sponsor ikun qed jikkometti reat li jibda prova klinika f'Malta kemm-il darba l-kumitat ta' l-Etika ma' jkunx ta' opinjoni favorevoli u l-Awtorità dwar il-Liċenzi ma tkunx informat lill-isponser bir- raġunijiet ghal nuqqas ta' aċċettazzjoni. Il-proċeduri sabiex isiru dawn id-deċiżjonijiet jistgħu jkunu hemm paralleli kemm le, skond ma jkun jiddependi mill-isponser.

Bidu ta' prova klinika.

(2) Qabel ma tinbeda xi prova klinika f'Malta l-isponser ghandu jipprezenta lill-Awtorità dwar il-Liċenzi talba valida ghal awtorizzazzjoni biex jagħmel il-prova klinika.

(3) Jekk l-Awtorità dwar il-Liċenzi tavża tinnotifika lill-isponser bir-raġunijiet ghal-nuqqas ta' aċċettazzjoni, l-isponser jista', ghal darba wahda biss, jemenda l-kontenut tat-talba msemmija fis-subregolament (2) biex tinghata kull l-konsiderazzjoni dovuta tar-raġunijiet mogħtija. Jekk l-isponser jonqos milli hekk jemenda t-talba, skond dan, it-talba ghandha titqies bhala rifjutata u l-prova klinika ma tkunx tista' tinbeda.

(4) (a) Konsiderazzjoni ta' talba valida għall-awtorizzazzjoni mill-Awtorità dwar il-Liċenzi ghandha ssir kemm jista' jkun malajr u ma ghandhiex teċċedi s-60 jum.

(b) Ebda estensjoni ohra għall-perjodu msemmi fil-paragrafu (a) ta dan is-subregolament ma ghandha tkun permessa hliet fil-każ ta' provi li jinvolvu l-prodotti mediċinali elenkati fil-subregolament (6), ta' dan ir-regolament li dwarhom estensjoni b'massimu ta' 30 jum ghandha tkun permessa. Ghal dawn il-prodotti, dan il-perjodu ta' 90 jum jista' jittawwal b'90 jum iehor fil-każ ta' konsultazzjoni ta' xi grupp jew tal-Kumitat ta' l-Etika. Fil-każ ta' terapija ta' ċelluli żenoġeniċi, ma ghandu jkun hemm ebda limitu ta' żmien għall-perjodu ta' awtorizzazzjoni.

(c) L-Awtorità dwar il-Liċenzi, tista' waqt il-perjodu ta' l-eżami ta' l-applikazzjoni, titlob informazzjoni supplimentari ma' dik diġa' pprezentanta mill-applikant. Il-perjodu stabbilit fil-paragrafi (a) u (b) ta' dan is-subregolament ikun sospiż sakemm tasal l-informazzjoni supplimentari.

(5) Mingħajr preġudizzju għas-subregolament (6), tista' tintalab awtorizzazzjoni bil-miktub qabel ma jinbdew provi klinici għal

dawk il-provi fuq prodotti mediċinali li ma jkollhomx awtorizzazzjoni ghat-tqeghid fis-suq skond il-kuntest ta' l-Att ta' l-2003 dwar il-Mediċini 2003, u r-regolamenti magħmulin tahtu, u li huma msemmin fil-Parti A ta' l-Anness mar-Regolamenti (KEE) Nru 2309/93, u prodotti oħra mediċinali b'karatteristiċi speċjali, bhal ma huma prodotti mediċinali li l-ingredjent attiv jew l-ingredjenti attivi tagħhom huma prodott bijoloġiku jew prodotti bijoloġiċi ta' oriġini mill-bniedem jew mill-annimali, jew li jkun fihom komponenti bijoloġiċi ta' oriġini mill-bniedem jew mill-annimali, jew li l-manifattura tagħhom tkun tinhtieg dawk il-komponenti.

(6) Ghandha tinhtieg awtorizzazzjoni bil-miktub qabel ma jinbdew provi kliniċi li jinvolvu prodotti mediċinali ghat-terapija tal-gene, terapija ta' ċelluli somatiċi inkluża terapija ta' ċelluli zenogeniċi u l-prodotti mediċinali kollha li jkun fihom organiżmi ġenetikament modifikati. Ebda provi ta' terapija tal-gene ma ghandhom jitwettqu li jirrizultaw f'tibdil ta' l-identità ġenetika tas-sugġett.

(7) Din l-awtorizzazzjoni ghandha tinhareg minghajr preġudizzju għall-applikazzjoni tad-Direttivi tal-Kunsill 90/219/KEE tat-23 ta' April, 1990 dwar l-użu kontenut ta' mikro-organiżmi ġenetikament modifikati u 2001/18/KEE tat-12 ta' Marzu, 2001 dwar rilaxx deliberat fl-ambjent ta' organiżmi ġenetikament modifikati.

Kif issir prova klinika.

**10.** Jistgħu jsiru emendi dwar kif issir prova klinika skond il-proċeduri deskritti hawn 'il quddiem:

(a) (i) Wara li tinbeda l-prova klinika, l-isponser jista' jagħmel emendi fil-protokoll. Jekk dawn l-emendi jkunu sostanzjali u x'aktarx li jista' jkollhom impatt fuq is-sigurtà tas-sugġetti taht prova jew ibiddu l-interpretazzjoni tad-dokumenti xjentifiċi li jsostnu kif issir l-prova, jew jekk ikunu sinifikanti b'xi mod ieħor, l-isponser għandu jinnotifika lill-Awtorità dwar il-Liċenzi u l-awtoritajiet kompetenti ta' l-Istati Membri involuti bir-raġunijiet ta', u l-kontenut ta', dawn l-emendi u għandu jinforma lill-Kumitat ta' l-Etika jew lill-kumitati involuti skond ir-regolamenti 7 u 9, u meta jkun mehtieg.

(ii) għandu jinkiseb kunsens informat ġdid irid jingieb minghand is-sugġetti tal-prova, jekk ikun hekk mehtieg li jsir mill-Kumitat ta' l-Etika;

(b) Fuq il-baži tad-dettalji msemmin ir-regolament 7 (2) u skond regolament 8, il-Kumitat ta' l-Etika għandu jagħti opinjoni fi żmien massimu ta' 35 jum mid-data li fiha jirċievi l-emenda proposta fil-forma tajba u kif imiss. Jekk din l-opinjoni ma tkunx

favorevoli, l-isponser m'ghandux jimplimenta l-emenda għall-protokoll. Jekk l-opinjoni tal-Kumitat ta' l-Etika tkun favorevoli u l-Awtorità dwar il-Liċenzi ma tkun qajmet ebda raġuni għannuqqas ta' aċċettazzjoni ta' l-emendi sostanzjali msemija hawn qabel, għandu jgħaddi biex jagħmel l-prova klinika skond il-protokoll kif emendat. Jekk dan ma jkunx il-każ, l-isponser għandu jew iqis ir-raġunijiet għannuqqas ta' aċċettazzjoni u jaddatta l-emenda proposta għall-protokoll, jew inkella jirtira l-emenda proposta.

(c) Mingħajr l-ebda preġudizzju għas-subregolamenti (1) u (2) ta' dan ir-regolament, fid-dawl taċ-ċirkostanzi notevolment f'okkorenza ta' avveniment ġdid relatat mal-għamil tal-prova jew l-izvilupp ta' prodott mediċinali investigattiv, meta dik il-ġrajja ġdida tista' x'aktarx toqot s-sigurezza tas-suġġetti, l-isponser u l-investigatur għandhom jiehdu l-miżuri tas-sigurezza addattati, u urġenti li jkunu jinkludu informazzjoni lis-suġġetti, biex jiproteġi lis-suġġetti minn kull periklu mmedjat. L-isponser għandu minnu fih jinforma lill-Awtorità dwar il-Liċenzi, u lill-Awtoritajiet kompetenti ta' l-Istati Membri involuti b'dawk l-avvenimenti ġoda u bil-miżuri mittieħda u għandu jiżgura li l-Kumitat ta' l-Etika gie mgharraf fl-istess hin, u

(d) Fi żmien 90 jum mit-tmiem ta' prova klinika l-isponser għandu javża lill-Awtorità dwar il-Liċenzi u lill-Awtoritajiet kompetenti ta' Istati Membri involuti u lill-Kumitat ta' l-Etika, li l-prova klinika tkun intemmet. Jekk il-prova jkollha timtemm kmieni, dan il-perjodu għandu jitnaqqas għal 15-il jum u r-raġunijiet għal dan jiġu mfissra b'mod ċar.

**11.** (1) Meta il-prova klinika tkun qed issir f'Malta, l-Awtorità dwar il-Liċenzi għandha ddahhal f'*database* Ewropea, aċċessibbli biss għall-awtoritajiet kompetenti ta' l-Istati Membri, ta' l-Aġenzija u ta' l-Kummissjoni:

Skambju ta' tagħrif.

(a) siltiet mit-talba għall-awtorizzazzjoni msemija fir-regolament 9(2);

(b) kull emenda magħmula għat-talba, kif provdut dwarha fir-regolament 9(3);

(c) kull emenda magħmula għall-protokoll, kif provdut dwarha fis-sub-regolamenti (1) u (2) tar-regolament 10;

(d) l-opinjoni favorevoli tal-Kumitat ta' l-Etika;

(e) id-dikjarazzjoni tat-tmiem tal-prova klinika; u

(f) referenza għall-ispezzjonijiet imwettqa dwar il-konformità ma' prattika ta' klinika tajba.

(2) Fuq talba sostanzjata ta' xi Stat Membru, l-Aġenzija jew il-Kummissjoni, l-Awtorità dwar il-Liċenzi għandha tipprovdi dak it-tagħrif addizzjonali kollu li jirrigwarda l-prova klinika in kwistjoni barra mit-tagħrif għa mdahhal fid-*database* Ewropea.

Sospensjoni tal-prova jew ksur.

**12.** (1) Meta l-Awtorità dwar il-Liċenzi jkollha raġunijiet oġġettivi biex tikkonsidra li l-kondizzjonijiet fit-talba għall-awtorizzazzjoni msemmija fir-regolament 9(2) ma għadhom jkunux aktar qed jitharsu jew ikollu xi tagħrif li jqajjem dubji dwar is-sigurtà jew validità xjentifika tal-prova klinika, jista' jissospendi jew jipprojbixxi l-prova klinika u għandu jinnotifika b'dan lill-isponser. Qabel ma Awtorità dwar il-Liċenzi tasal għad-deċiżjoni tagħha hija għandha, hlief meta jkun hemm riskju imminenti, titlob lill-isponser u, jew lill-investigatur għall-opinjoni tagħhom, li għandha tinghata fi żmien ġimgħa. F'dan il-każ, l-Awtorità dwar il-Liċenzi involuta għandha minnufih tinforma lill-Awtoritajiet kompetenti l-oħra, lill-Kumitat ta' l-Etika involuti, lill-Aġenzija u lill-Kummissjoni bid-deċiżjoni tagħha li tissospendi jew li tipprojbixxi l-prova u bir-raġunijiet għal din id-deċiżjoni.

(2) Meta Awtorità dwar il-Liċenzi jkollha raġunijiet oġġettivi biex tikkonsidra li l-isponser jew l-investigatur jew xi persuna oħra involuta fit-tmexxija tal-prova ma tkunx aktar tissodisfa l-obbligi stipulati, hija għandha minnufih tinformah b'dan, filwaqt li tindika l-kors ta' azzjoni li għandu jiehu biex jirrimedja din is-sitwazzjoni. L-Awtorità dwar il-Liċenzjar kompetenti involuta għandha minnufih tinforma lill-Kumitat ta' l-Etika, lill-awtoritajiet kompetenti l-oħra u lill-Kummissjoni b'din l-azzjoni.

Awtorizzazzjoni għall-manifattura u l-importazzjoni ta' prodotti mediċinali investigattivi.

**13.** (1) Ma tista' issir ebda manifattura jew importazzjoni ta' prodott mediċinali investigattivi kem-il-darba ma jkunx hemm awtorizzazzjoni għal dik l-attività mehtieġa mill-Awtorità dwar il-Liċenzi.

Iżda l-awtorizzazzjoni tinghata bil-kondizzjoni li jitwettqu l-obbligi imposti minnha fuq dawn l-attivittajiet. Din l-awtorizzazzjoni tkun mehtieġa ukoll jekk il-prodotti mediċinali investigattivi jkunu intiżi għall-esportazzjoni.

(2) (a) L-awtorizzazzjoni hija mehtieġa kemm għall-manifattura totali kemm għal dak parzjali u għall-proċessi varji ta' taqsim, ippakkettjar jew prezentazzjoni.

(b) Madanakollu, l-Awtorità dwar il-Liċenzi tista teskludi mis-subregolament (1) il-proċess li jsir tibdil fl-ippakkjar ta' prodotti mediċinali investigattivi meta dan il-proċess isir minn spizjara jew persuni awtorizzati biex jeseġwixxu dawk il-proċessi fl-isptar, ċentru tas-Sahha jew klinika fejn dak il-prodott mediċinali investigattiv ikun intiż sabiex jintuża fihom biss.

(3) Id-detentur ta' l-awtorizzazzjoni għandu jiddesponi mill-prodotti mediċinali investgattivi skond il-pattijiet tal-kondizzjonijiet imposti mill-Awtorità dwar il-Liċenzi.

**14.** (1) Id-detentur ta' l-awtorizzazzjoni msemmija fir-regolament 13 għandu jkollu għad-disposizzjoni permanentementi u kontinwa, tiegħu is-servizz ta' mill-anqas persuna wahda kwalifikata li jkollha bil-kwalifiki u l-esperjenza mfissra taht ir-Regolament ta' l-2004 dwar il-Manifattura ta' Prodotti Mediċinali għal Użu mill-Bniedem, u huwa jkun responsabbli biex jeseġwixxi id-dmirijiet speċifikati fis-subregolament(2) ta' dan ir-regolament.

Manifattura u importazzjoni ta' prodotti mediċinali investigattivi.

(2) B'żieda mad-doveri tiegħu kif inhuma definiti taht ir-Regolament ta' l-2004 dwar il- Manifattura ta' Prodotti Mediċinali għal-Użu mill-Bniedem, il-persuna kwalifikata għandha ukoll, għall-finijiet ta' dawn ir-regolamenti, tkun responsabbli biex tiżgura li:

(a) fil-każ ta' prodotti mediċinali investigattivi manifatturati f'Malta, kull lott ta' prodotti mediċinali ikun ġie manifatturat u verifikat konformement mal-prinċipji u l-linji gwida għall-Prattika ta' Manifattura Tajba imwaqqfa il-liġi fis-sehħ, l-inkartament dwar l-ispeċifikazzjoni tal-prodott u t-tagħrif avżat skond regolament 9(2) ta' dawn ir-regolamenti;

(b) fil-każ ta' prodotti mediċinali investigattivi manifatturati f'pajjiż terz, li kull lott ta' produzzjoni jkun ġie manifatturat u verifikat skond l-istandards ta' prattika tajba ta' manifattura ta' l-anqas ekwivalenti għal dawk stipulati b'liġijiet fis-sehħ, skond l-inkartament ta' l-ispeċifikazzjoni tal-prodott, u li kull lott ta' produzzjoni jkun ġie verifikat skond it-tagħrif avżat konformement skond mar-regolament 9(2) ta' dawn ir-regolamenti.

(ċ) fil-każ ta' prodott mediċinali investigattiv li huwa prodott li jista' jintuża biex jitqabbel ma' prodott iehor minn pajjiż terz, u li jkollu awtorizzazzjoni ta' tqeghid fis-suq, meta d-

dokumentazzjoni li tiċċertifika li kull lott ta' produzzjoni ikun ġie manifatturat ta' l-anqas f'kondizzjonijiet ekwivalenti għall-standards ta' prattika tajba ta' manifattura msemmija hawn qabel ma tkunx tista' tinkiseb, kull lott ta' produzzjoni jkun għadda mill-analizi, testijiet u verifiki relevanti kollha meħtieġa biex jikkonfermaw il-kwalità tiegħu skond it-tagħrif avżat konformement mar-regolament 9(2) ta' dawn ir-regolamenti.

(3) Sa fejn id-dispożizzjonijiet stipulati fil-paragrafu (a), (b) jew (c) tas-subregolament (2) ikunu mharsa, prodotti mediċinali investigattivi m'għandhomx jgħaddu minn aktar verifiki jekk dawn jiġu importati fi Stat Membru iehor flimkien ma' ċertifikazzjoni tar-rilaxx tal-lott iffirmit minn persuna kwalifikata.

Fil-każijiet kollha, il-persuna kkwalifikata għandha tiċċertifika f'reġistru jew f'dokument ekwivalenti li kull lott manifatturat jissodisfa d-dispożizzjonijiet ta' dan ir-regolament. Dan ir-registru jew dokument ekwivalenti għandu jinżamm aġġornat, waqt li dawn l-operazzjonijiet ikunu qegħdin isiru u għandu jibqa' għad-dispożizzjoni ta' l-Awtorità dwar il-Liċenzi għal perjodu ta' hames snin.

Tikkettjar.

**15.** (1) Il-partikolaritajiet fuq il-pakkettjar ta' barra ta' prodotti investigattivi, jew fejn m'hemmx ippakkettjar ta' barra, fuq il-pakkettjar immedjat għandu jidher f'almenu f'wahda mill-lingwi ufficjali ta' Malta, u jrid ikun konformi mal-linji gwida ta' prattika tal-manifattura tajba għal prodotti mediċinali investigattivi ppubblikati mill-Kommissjoni.

Il-verifika ta' konformità ta' prodotti mediċinali investigattivi bi prattika ta' klinika u ta' manifattura tajba.

**16.** (1) (a) Biex tiġi verifikata l-konformità mad-dispożizzjonijiet dwar prattika tajba ta' klinika u ta' manifattura, l-Awtorità dwar il-Liċenzi għandha tahtar spetturi biex f'isem il-Komunità jagħmlu spezzjonijiet u jispezzjonaw is-siti involuti b' kull prova klinika mwettqa, b'mod partikolari s-sit jew siti ta' prova, is-sit tal-manifattura tal-prodott mediċinali investigattiv, kull laboratorju wżat għall-analizi fil-prova klinika u, jew fil-post ta' l-isponser.

(b) L-Awtorità dwar il-Liċenzi għandha tinforma lill-Agenzija, bl-ispezzjonijiet li jkunu saru u r-rizultati għandhom jingħataw għarfien mill-Istati Membri l-oħra kollha.

(ċ) Dawn l-ispezzjonijiet għandhom ikunu koordinati mill-Agenzija, fil-kuntest tas-setgħat tagħha kif hemm provdut dwarhom fir-Regolament (KEE) Nru 2309/93. Stat Membru jista' jitlob għajnuma minn Stat Membru iehor f'din il-materja.

(2) Wara li tkun saret l-ispezzjoni, għandu jithejja rapport. Ir-rapport għandu jkun disponibbli għall-isponser waqt li jkunu

salvagwardati l-aspetti ta' konfidenzjalità. Jista' jkun disponibbli għall-Istati Membri l-oħra, għall-Kumitat l-Etika u għall-Aġenzija, fuq talba motivata tagħhom.

**17.** (1) L-investigatur għandu jirrapporta kull ġrajja serja kuntrarja minnufih lill-isponser hlief għal dawk fejn il-protokoll jew il-*brochure* ta' l-investigatur jidentifikahom bhala li ma jehtigux rapportar immedjat. Ir-rapport immedjat għandu jiġi segwit b'rapporti dettaljati, bil-miktub. Ir-rapporti immedjati u dawk li jiġu wara għandhom jidentifikaw is-suġġetti b'numri uniċi ta' kodiċi mogħtija lil dawn ta' l-aħhar.

Avviż ta' ġrajjet kuntrarji.

(2) ġrajjet kuntrarji u, jew anormalitajiet tal-laboratorju identifikati fil-protokoll bhala kritiċi għall-valutazzjoni ta' sigurtà, għandhom jiġu rapportati lill-isponser skond il-htigiet ta' rapportaġġ u fit-termini żmien speċifikati fil-protokoll.

(3) Dwar rapporti dettaljati ta' mewt ta' xi suġġett, l-investigatur għandu jagħti lill-isponser u lill-Kumitat ta' l-Etika kull tagħrif addizzjonali mitlub.

(4) L-isponser għandu jżomm *records* dettaljati tal-ġrajjet kuntrarji kollha li jiġu rapportati lill-investigatur jew investigaturi. Dawn ir-*records* għandhom jintbagħtu lill-Istati Membri li fit-territorju tagħhom tkun qed titmexxa l-prova klinika, jekk dawn hekk jitolbu.

**18.** (1) (a) L-isponser għandu jiżgura li t-tagħrif kollu relevanti dwar reazzjonijiet kuntrarji serji suspettati u mhux mistennija li jkunu fatali jew ta' theddida għall-ħajja, jiġi registrat u rrapportat kemm jista' jkun malajr lill-awtoritajiet kompetenti fl-Istati Membri kollha involuti, u lill-Kumitat ta' l-Etika, u f'kull każ mhux aktar tard minn sebat ijiem wara li l-isponser isir jaf b'dak il-każ, u li t-tagħrif relevanti li jiġi wara jiġi sussegwentement komunikat fi żmien tmint ijiem oħra.

Avviż ta' reazzjonijiet kuntrarji serji.

(b) Kull reazzjoni kuntraja serja suspettata u mhux mistennija oħra għandha tiġi rapportata lill-awtoritajiet kompetenti involuti u lill-Kumitat ta' l-Etika involuti kemm jista' jkun malajr, iżda fi żmien massimu ta' hmistax-il jum minn mindu l-isponser ikun sar jaf bih l-ewwel darba.

(ċ) l-Awtorità dwar il-Licenzi għandha tiżgura li r-reazzjonijiet kuntrarji serji suspettati u mhux mistennija kollha dwar prodott mediċinali investigattiv li jingiebu għall-attenzjoni tagħha, għandhom jiġu registrati.

(d) L-isponser ghandu jinforma wkoll lill-investigaturi kollha.

(2) Darba fis-sena matul il-prova klinika, l-isponser ghandu jaghti lill-Istati Membri li fit-territorju taghhom tkun qed titmexxa l-prova klinika, u lill-Kumitat ta' l-Etika, elenku tar-reazzjonijiet kuntrarji serji suspettati kollha li jkunu sehew matul dan il-perjodu u rapport dwar is-sigurtà tas-sugġetti.

(3) l-Awtorità dwar il-Licenzi ghandha tara li r-reazzjonijiet kuntrarji serji suspettati u mhux mistennija ghal prodott medicinali investigattiv li jingiebu ghall-attenzjoni tieghu jiġu minnufih imdahhla f' *database* Ewropea li fiha jkunu biss l-awtoritajiet kompetenti ta' l-Istati Membri, ta' l-Aġenzija u tal-Kummissjoni li jkollhom dhul skond ir-regolament 11 (1).

(4) Il-ġbir, verifika u prezentazzjoni ta' rapporti ta' ġrajjet kuntrarji jew dwar proceduri ta' deċifrar ghal reazzjonijiet kuntrarji serji mhux mistennija ghandhom isiru skond il-linji gwida dettaljati ppubblikat mill-Kommissjoni.

Disposizzjonijiet  
generali.

**19.** (1) Dawn ir-regolamenti huma minghajr preġudizzju ghal kull responsabbiltà civili u kriminali ta' l-isponser jew tal-investigatur. Ghal dan il-ghan, l-isponser jew rappreżentant legali ta' l-isponser ghandhom ikunu stabbiliti fil-Komunità.

(2) Sakemm l-Awtorità dwar il-Licenzi ma tkunux ghadha stabbiliet kondizzjonijiet preċiżi dwar ċirkostanzi eċċezzjonali, prodotti medicinali investigattivi u, il-mekkanizmi wżati ghall-amministrazzjoni taghhom ghandhom jintgħamlu disponibbli bis-sugġetti tal-prova bla hlas mill-isponser.

**L.N. 490 of 2004****MEDICINES ACT, 2003  
( ACT NO. III OF 2003)****Clinical Trials Regulations, 2004**

IN exercise of the powers conferred by article 106 of the Medicines Act, the Minister of Health, Elderly and Community Care has made the following regulations:-

**1.** The title of these Regulations is Clinical Trials Regulations, Title.  
2004.

**2.** (1) These regulations apply Directive 2001/20/EC and shall Scope.  
regulate the conduct of clinical trials, including multi-centre trials, in  
Malta on human subjects involving medicinal products as defined under  
the Act and in particular relating to the implementation of good clinical  
practice. These regulations shall not apply to non-interventional trials.

(2) All clinical trials including bioavailability and  
bioequivalence studies shall be designed, conducted and reported in  
accordance with the principles of good clinical practice. The various  
aspects associated with submissions including notifications and requests  
to the Licensing Authority and the Ethics Committee and any other  
procedures and requirements related to clinical trials as deemed  
necessary by the Licensing Authority, shall be in accordance with the  
publications related to clinical trials published and, or adopted  
periodically by the Commission as deemed necessary by the Licensing  
Authority.

**3.** In these regulations, unless the context otherwise requires :- Definitions.

“adverse event” means any untoward medical occurrence in  
a patient or clinical trial subject who is administered a medicinal  
product and which does not necessarily have a causal relationship  
with this treatment;

“adverse reaction” means all untoward and unintended  
responses to an investigational medicinal product related to any  
dose administered;

“Agency” means the European Medicines Agency established by Council Regulation (EC) No 726/2004;

“clinical trial” means any investigation in human subjects intended to discover or verify the clinical, pharmacological and, or other pharmacodynamic effects of any investigational medicinal product and, or to identify any adverse reactions to any investigational medicinal product and, or to study absorption, distribution, metabolism and excretion of any investigational medicinal product with the object of ascertaining its safety and, or efficacy. This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State;

“the Ethics Committee” means an independent body, consisting of healthcare professionals and non-medical members, whose responsibility is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to recruit and inform trial subjects and obtain their informed consent;

“good clinical practice” means a set of internationally recognized ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well being of trial subjects are protected and that the results of the clinical trials are credible;

“informed consent” means a decision, which must be written in one of the official languages of Malta or in a language understandable to the clinical trial subject and, or his legal representative, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if such person is unable to write, oral consent may be given in the presence of at least one witness;

“inspection” means the act by the Licensing Authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources deemed

to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and, or contract research organisation's facilities, or at other establishments which the Licensing Authority sees fit to inspect;

“investigational medicinal product” means a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

“investigator” means a doctor or a person who is suitably qualified approved by the Licensing Authority for investigations because of the scientific background and the experience in patient care such investigation requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;

“investigator's brochure” means a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects;

“multi-centre clinical trial” means a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and, or in Member States and third countries;

“non-interventional trial” means a study where a medicinal product is, prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

“protocol” means a document that describes the objective or objectives, design, methodology, statistical considerations and

organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;

“serious adverse” event or “serious adverse reaction” means any untoward medical occurrence or effect where any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

“sponsor” means an individual, company, institution or organisation or its legal representative who must be established in the Community and who takes responsibility for the initiation, management and, or financing of a clinical trial;

“subject” means an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;

“unexpected adverse reaction” means an adverse reaction, the nature or severity of which is not consistent with the relevant product information (e.g. investigator’s brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

Protection of  
clinical trial  
subjects.

**4.** (1) A clinical trial may be undertaken only if, in particular:

(a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and, or the Licensing Authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently and continuously monitored;

(b) the trial subject or, when the person is not able to give informed consent, his legal representative, has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time by revoking his informed consent without suffering any detriment;

(c) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in

accordance with the Data Protection Act and any amendments thereto, are safeguarded;

(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial. However if the individual is unable to write, oral consent may be given in the presence of at least one witness;

(e) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

(2) It shall be the responsibility of an appropriately named qualified doctor or, where appropriate, of a named qualified dentist or other named person with appropriate qualifications as the case may be, to provide at all times the necessary medical care and make medical decisions on behalf of the subjects.

(3) The subject shall be provided with a contact point where he may obtain further information.

**5.** Without prejudice to any other relevant restriction, a clinical trial on minors may only be undertaken if: Clinical trials on minors.

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to his capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is given due consideration by the investigator or, where appropriate, the principal investigator;

(d) no incentives or financial inducements are given except agreed compensation;

(e) some direct benefit for the group of patients is expected from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give

informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with pediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of pediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

Clinical trials on incapacitated adults not able to give informed legal consent.

**6. (1)** For the performance of clinical trials on persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving such consent shall also apply. Furthermore, clinical trials on incapacitated adults who have not given and not refused informed consent before the onset of their incapacity, shall only be allowed if:

(a) the informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject;

(b) the person not able to give informed legal consent has received information according to his capacity of understanding regarding the trial, the risks and the benefits;

(c) the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is given due consideration by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except agreed compensation;

(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers;

(f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;

(g) the Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

(h) the interests of the patient always prevail over those of science and society; and

(i) there are grounds for expecting that administering the medicinal product to be tested will benefit the patient outweighing the risks or produce no risk at all.

7. (1) The Licensing Authority shall set up an Ethics Committee Ethics Committee. which shall give its opinion, before a clinical trial commences, on any issue requested.

(2) In preparing its opinion, the Ethics Committee shall consider, in particular:

(a) the relevance of the clinical trial and the trial design;

(b) whether the evaluation of the anticipated benefits and risks as required under regulation 4 (1)(a) of these regulations is satisfactory and whether the conclusions are justified;

(c) the protocol;

(d) the suitability of the investigator and supporting staff;

(e) the investigator's brochure;

(f) the quality of the facilities;

(g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in regulation 4;

(h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;

(i) any insurance or indemnity to cover the liability of the investigator and sponsor;

(j) the amounts and, where appropriate, the arrangements for justly rewarding investigators and compensating trial subjects and the relevant aspects of any agreement between the sponsor and the site;

(k) the arrangements for the recruitment of subjects.

(3) (a) The Ethics Committee shall within a maximum of 60 days from the date of receipt of a valid application give its reasoned opinion to the applicant and the Licensing Authority.

(b) Within the period of examination of the application for an opinion, the Ethics Committee may send a single request for information supplementary to that already supplied by the applicant. The period mentioned in paragraph (a) shall be suspended until receipt of the supplementary information.

(4) No extension to the 60-day period referred to in sub-regulation (3) hereof shall be permissible except in the case of trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In this case, an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or committee. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

Single opinion.

**8.** (1) In the case of multi-centre clinical trials limited to the territory of Malta there shall only be in respect of such trials a single opinion by the Ethics Committee.

(2) In the case of multi-centre clinical trials which are carried out in more than one Member State simultaneously, a single

opinion shall be given by the Ethics Committee for each Member State concerned by the clinical trial.

9. (1) It shall be an offence for the sponsor to start a clinical trial in Malta unless the Ethics Committee has issued a favourable opinion and the Licensing Authority has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

Commencement of a clinical trial.

(2) Before commencing any clinical trial in Malta, the sponsor shall submit a valid request for authorisation to conduct the clinical trial to the Licensing Authority.

(3) If the Licensing Authority notifies the sponsor of grounds for non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in sub-regulation (2) in order to take due account of the grounds given. If the sponsor fails to amend the request accordingly, the request shall be considered rejected and the clinical trial may not commence.

(a) Consideration of a valid request for authorisation by the Licensing Authority shall be carried out as rapidly as possible and may not exceed 60 days.

(b) No further extensions to the period referred to in paragraph (a) hereof shall be permissible except in the case of trials involving the medicinal products listed in sub-regulation (6), hereof for which an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or of the Ethics Committee. In the case of xenogenic cell therapy there shall be no time limit to the authorisation period.

(c) Within the period of examination of the application the Licensing Authority may request information supplementary to that already supplied by the applicant. The period laid down in paragraphs (a) and (b) hereof shall be suspended until receipt of the supplementary information.

(5) Without prejudice to sub-regulation (6), written authorisation may be required before the commencement of clinical trials for such trials on medicinal products which do not have a marketing authorisation within the meaning of the Medicines Act, 2003 and any regulations thereunder, and are referred to in Part A of the Annex to Regulation (EEC) No 2309/93, and other medicinal products with special characteristics, such as medicinal products the active ingredient or active

ingredients of which is or are a biological product or biological products of human or animal origin, or contain biological components of human or animal origin, or the manufacturing of which requires such components.

(6) Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

(7) This authorisation shall be issued without prejudice to the application of Council Directives 90/219/EEC of the 23rd April, 1990 on the contained use of genetically modified micro-organisms and 2001/18/EEC of the 12th March, 2001 on the deliberate release into the environment of genetically modified organisms.

Conduct of a clinical trial.

**10.** Amendments may be made to the conduct of a clinical trial following the procedure described hereinafter:

(a) (i) After the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall preferably prior to implementation notify the Licensing Authority and the competent authorities of the Member States concerned of the reasons for, and content of, these amendments and shall inform the Ethics Committee or committees concerned in accordance with regulations 7 and 9, and where necessary;

(ii) A new informed consent has to be obtained from the trial subjects if so required by the Ethics Committee;

(b) The Ethics Committee shall, on the basis of the details referred to in regulation 7 (2) and in accordance with regulation 8, give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form. If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol. If the opinion of the Ethics Committee is favourable and the Licensing Authority has raised no grounds for non-acceptance of the abovementioned substantial amendments, the sponsor shall proceed to conduct the clinical trial following the amended protocol. Should this not be the case, the sponsor shall

either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or otherwise withdraw the proposed amendment;

(c) Without prejudice to sub-regulations (1) and (2) of this regulation, in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures which include information to the subjects, in order to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the Licensing Authority and the competent authorities of the Member States concerned of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time; and

(d) Within 90 days of the end of a clinical trial the sponsor shall notify the Licensing Authority and the competent authorities of the Member States concerned and the Ethics Committee, that the clinical trial has ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

**11.** (1) When the clinical trial is taking place in Malta, the Licensing Authority shall enter in a European database, accessible only to the competent authorities of the Member States, the Commission and the Agency:

Exchange of Information.

(a) extracts from the request for authorisation referred to in regulation 9 (2);

(b) any amendments made to the request, as provided for in regulation 9 (3);

(c) any amendments made to the protocol, as provided for in sub-regulations (1) and (2) of regulation 10;

(d) the favourable opinion of the Ethics Committee;

(e) the declaration of the end of the clinical trial; and

(f) a reference to the inspections carried out on conformity with good clinical practice.

(2) At the substantiated request of any Member State, the Agency or the Commission, the Licensing Authority shall supply all further information concerning the clinical trial in question other than the data already in the European database.

Suspension of the trial or infringements.

**12.** (1) Where the Licensing Authority has objective grounds for considering that the conditions in the request for authorisation referred to in regulation 9 (2) are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof. Before the Licensing Authority reaches its decision it shall, except where there is imminent risk, ask the sponsor and, or the investigator for their opinion, to be delivered within one week. The Licensing Authority shall forthwith inform the other competent authorities, the Ethics Committee concerned, the Agency and the Commission of its decision to suspend or prohibit the trial and of the reasons for the decision.

(2) Where the Licensing Authority has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The Licensing Authority shall forthwith inform the Ethics Committee, the other competent authorities and the Commission of this course of action.

Authorisation for the manufacture and import of investigational medicinal products.

**13.** (1) It shall not be lawful to manufacture or import any investigational medicinal product unless there is in respect of such an activity an authorisation issued by the Licensing Authority;

Provided that the authorisation shall be conditional to the carrying out of such obligations as may be imposed therein. This authorization shall also be required if the investigational medicinal product or products is, are intended for export.

(2) (a) The authorisation shall be required for both total and partial manufacture and for the various processes of dividing up, packaging or presentation.

(b) However, the Licensing Authority may exclude from sub-regulation (1) the process of making changes to the packaging of investigational medicinal products where this process is carried out by pharmacists or persons authorised to carry out such processes in hospital, health centre or clinic within which solely such investigational medicinal products are intended for use.

(3) The holder of the authorisation shall dispose of investigational medicinal products in terms of the conditions imposed by the Licensing Authority.

**14.** (1) The holder of the authorisation referred to in regulation 13 shall have at his continuous and permanent disposal the services of at least one qualified person having the qualifications and experience defined under the Manufacture of Medicinal Products for Human Use Regulations 2004, and he shall be responsible for carrying out the duties specified in sub-regulation (2) hereof..

Manufacture and import of investigational medicinal products.

(2) In addition to his duties defined under the Manufacture of Medicinal Products for Human Use Regulations, 2004, the qualified person shall also, for the purposes of these regulations, be responsible for ensuring that:

(a) in the case of investigational medicinal products manufactured in Malta, each batch of medicinal products has been manufactured and checked in compliance with the principles and guidelines of Good Manufacturing Practice laid down by the law in force, the product specification file and the information notified pursuant to regulation 9 (2) of these regulations;

(b) in the case of investigational medicinal products manufactured in a third country, each production batch has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down by the law in force, in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to Regulation 9 (2) of these Regulations;

(c) in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to above cannot be obtained, each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information notified pursuant to regulation 9 (2) of these regulations.

(3) Insofar as the provisions laid down in paragraph (a), (b), or (c) of sub-regulation (2) are complied with, investigational medicinal products shall not have to undergo any further checks if they

are imported into another Member State together with batch release certification signed by the qualified person.

(4) In all cases, the qualified person shall certify in a register or equivalent document that each production batch satisfies the provisions of this regulation. The said register or equivalent document shall be kept up to date as operations are carried out and shall remain at the disposal of the Licensing Authority for a period of five years.

Labelling.

**15.** The particulars on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging shall appear in at least one of the official languages of Malta and shall comply with the guidelines of good manufacturing practice for investigational medicinal products published by the Commission.

Verification of compliance of investigational medicinal products with good clinical and manufacturing practice.

**16.** (1) (a) To verify compliance with the provisions on good clinical and manufacturing practice, the Licensing Authority shall appoint inspectors who shall on behalf of the Community carry out inspections and inspect the sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and, or the sponsor's premises.

(b) The Licensing Authority shall inform the Agency of the inspections carried out and the results shall be recognised by all the other Member States.

(c) These inspections shall be coordinated by the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93. A Member State may request assistance from another Member State in this matter.

(2) After an inspection is performed an inspection report shall be drawn up. The report shall be made available to the sponsor while safeguarding confidential aspects. It may be made available to the other Member States, to the Ethics Committee and to the Agency, at their reasoned request.

Notification of adverse events.

**17.** (1) The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

(2) Adverse events and, or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

(3) For reported death of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

(4) The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request.

**18.** (1) (a) The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

Notification of serious adverse reactions.

(b) All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

(c) The Licensing Authority shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention, shall be recorded.

(d) The sponsor shall also inform all investigators.

(2) Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and to the Ethics Committee, with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

(3) The Licensing Authority shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which, only the competent authorities of the Member States, the Agency and the Commission shall have access in accordance with regulation 11 (1).

(4) The collection, verification and presentation of adverse event or reaction reports together with the decoding procedures for unexpected serious adverse reactions shall be carried out in accordance with the detailed guidance published by the Commission.

General provisions.

**19.** (1) These regulations are without prejudice to the civil and criminal liability of the sponsor or investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community.

(2) Unless the Licensing Authority has established precise conditions for exceptional circumstances, investigational medicinal products and, or the devices used for their administration shall be made available free of charge by the sponsor to the trial subjects.