参考資料３－１

平成 25 年 5 月 21 日

厚生労働大臣　殿

一般社団法人 日本救急医学会
代表理事　行岡

日本小児救急医学会
理事長　市川 光太郎

一般社団法人　日本循環器学会
循環器救急医療委員会蘇生科学小委員会
委員長　長尾

疫学研究に関する倫理指針及び臨床研究に関する倫理指針の見直しにあたっての救急医学領域での対応についての検討の要望

「臨床研究に関する倫理指針の見直しにあたり、救急医学領域での対応についての検討の要望」（平成 24 年 12 月 12 日）を一般社団法人日本救急医学会より提出さていただきましたが、重ねて、救急医療、特に、重症・重篤例における患者同意（インフォームド・コンセント）の取得・免除（Waved Informed Consent）等の課題についてご検討を要望致します。

救急医療における臨床研究ならびに疫学研究での患者同意の手続きに関する課題：

- 患者本人に意識が無いなどの理由で本人がインフォームド・コンセントの対象となりえないことが多いこと
- 代諾者を見つけることは困難で、いたとしても、差し迫った状況で適切な代諾者であるか否か判断することが困難であること
- 患者本人もしくは代諾者から署名で同意を得たとしても、差し迫った状況下での説明と同意では、その同意の実質的な信頼性についての懸念が払拭できないこと
- 研究のためのインフォームド・コンセントの手続きに時間を費やすと患者の不利益につながりかねないこと

臨床研究は、国民の生命と健康を守り増進めざすために行われますが、時間的制約が極めて厳しい救急医療の領域でも、社会に受入れられるかたちで臨床研究が実施できる体制が是非とも必要です。

今回の倫理指針の見直しにあたっては、「医薬品の臨床試験の実施の基準に関する省令」（平成 9 年厚生省令第 28 号）第 55 条に定める緊急状況下における救命的治験に準じて、緊急状況下における臨床試験への参加について、規定を設けていただけますようよろしくお願い申し上げます。

参考資料３－２

（別添）

臨床研究に関する倫理指針

平成１５年７月３０日
（平成１６年１２月２８日全部改正）
（平成２０年７月３１日全部改正）

厚　生　労　働　省

第４　インフォームド・コンセント

＜細則＞

被験者又は代諾者等に対する説明事項は、一般的に以下のとおりとする。ただし、臨床研究の内容に応じて変更できるものとする。

イ　当該臨床研究への参加は任意であること

ロ　当該臨床研究への参加に同意しないことをもって不利益な対応を受けないこと

ハ　被験者又は代諾者等は、自らが与えたインフォームド・コンセントについて、いつでも不利益を受けることなく撤回することができること

ニ　被験者として選定された理由

ホ　当該臨床研究の意義、目的、方法及び期間

ヘ　研究者等の氏名及び職名

ト　予測される当該臨床研究の結果、当該臨床研究に参加することにより期待される利益及び起こり得る危険並びに必然的に伴う心身に対する不快な状態、当該臨床研究終了後の対応

チ　被験者及び代諾者等の希望により、他の被験者の個人情報保護や当該臨床研究の独創性の確保に支障がない範囲内で、当該臨床研究計画及び当該臨床研究の方法に関する資料を入手又は閲覧することができること

リ　個人情報の取扱い、提供先の機関名、提供先における利用目的が妥当であること等について倫理審査委員会で審査した上で、当該臨床研究の結果を他の機関へ提供する可能性があること

ヌ　当該臨床研究の成果により特許権等が生み出される可能性があること及び特許権等が生み出された場合のその権利等の帰属先

ル　被験者を特定できないように対処した上で、当該臨床研究の成果が公表される可能性があること

ヲ　当該臨床研究に係る資金源、起こり得る利害の衝突及び研究者等の関連組織との関わり

ワ　試料等の保存及び使用方法並びに保存期間

カ　当該臨床研究に関する問い合わせ、苦情等の窓口の連絡先等に関する情報

ヨ　第１の３(1)①に規定する研究（体外診断を目的とした研究を除く。）にあっては、当該臨床研究に伴い被験者に生じた健康被害の補償のための保険等必要な措置（第１の３(1)①に規定する研究のうち体外診断を目的とした研究及び第１の３(1)②に規定する研究にあっては、補償の有無。）

タ　観察研究にあっては、試料等の採取が侵襲性を有する場合には、補償のための保険等必要な措置の有無等十分な説明の上、インフォームド・コンセントを受けるよう留意すること。

【被験者からインフォームド・コンセントを受けることが困難な場合】

レ　当該臨床研究の重要性及び被験者の当該臨床研究への参加が当該臨床研究を実施するにあたり必要不可欠な理由

１　被験者からインフォームド・コンセントを受ける手続

（１）研究者等は、臨床研究を実施する場合には、被験者に対し、当該臨床研究の目的、方法及び資金源、起こりうる利害の衝突、研究者等の関連組織との関わり、当該臨床研究に参加することにより期待される利益及び起こりうる危険、必然的に伴う不快な状態、当該臨床研究終了後の対応、臨床研究に伴う補償の有無その他必要な事項について十分な説明を行わなければならない。

＜細則＞

本項及び細則の「起こり得る利害の衝突」とは、いわゆる利益相反（Conflict of Interest：COI）のことをいうものである。

利益相反（Conflict of Interest：COI）については、「利益相反ワーキング・グループ　報告書」（平成１４年１１月１日　文部科学省科学技術・学術審議会技術・研究基盤部会産学官連携推進委員会利益相反ワーキンググループ）、「臨床研究の利益相反ポリシー策定に関するガイドライン」（平成１８年３月　文部科学省）及び「厚生労働科学研究

における利益相反（Conflict of Interest:COI）の管理に関する指針」（平成２０年３月３１日科発第0331001号厚生科学課長決定）が参考になるため、利益相反（Conflict of Interest：COI）の管理については、当該報告書、ガイドライン及び指針に留意すること。

（２）インフォームド・コンセントを受ける手続については、臨床研究の多様な形態に配慮し、以下の方法によることとする。

① 介入を伴う研究の場合

研究者等は、被験者が（１）の規定により文書により説明した内容を理解していることを確認した上で、自由意思によるインフォームド・コンセントを文書で受けなければならない。

② 観察研究の場合

ア 人体から採取された試料等を用いる場合

研究者等は、文書により説明し、文書により同意を受ける方法により、被験者からインフォームド・コンセントを受けなければならない。ただし、試料等の採取が侵襲性を有しない場合には、文書による説明及び文書による同意に代えて、説明の内容及び被験者から受けた同意に関する記録を作成することができる。

イ 人体から採取された試料等を用いない場合

研究者等は、被験者からインフォームド・コンセントを受けることを必ずしも要しない。この場合において、研究者等は、当該臨床研究の目的を含む研究の実施についての情報を公開しなければならない。

＜細則＞

インフォームド・コンセントを受けない場合に、当該臨床研究の実施について情報公開する場合は、以下の事項が含まれていること。なお、これらの事項については、研究計画に記載すること。

① 当該研究の意義、目的、方法
② 研究機関名
③ 保有する個人情報に関して第２の２(12)③、④又は⑥の規定による求めに応じる手続（第２の４(4)の規定により手数料の額を定めたときは、その手数料の額を含む）
④ 保有する個人情報に関して、第２の１(7)⑩の規定による、問い合わせ、苦情等の窓口の連絡先に関する情報
⑤ 第２の２(12)③二の利用目的の通知、④の規定による開示又は⑦の規定による理由の説明を行うことができない場合は当該事項及びその理由

（３）第１の３（１）①に規定する研究（体外診断を目的とした研究を除く。）を実施する場合には、当該臨床研究の実施に伴い被験者に生じた健康被害の補償のための保険その他の必要な措置の内容について、事前に十分な説明を行い、被験者の同意を受けなければならない。

＜細則＞

臨床研究に関連して被験者に健康被害が生じた場合の補償のための保険等必要な措置は、必ずしも研究者等による金銭の支払いに限られるものではなく、健康被害に対する医療の提供及びその他の物又はサービスの提供という手段が含まれるものである。

なお、被験者に健康被害が生じた場合でも、研究者等に故意・過失がない場合には、研究者等は必ずしも金銭的な補償を行う義務が生ずるものではない。ただし、補償金が保険により填補される場合や、当該臨床研究において被験者の受ける便益及び被験者の負担するリスク等を評価し被験者の負担するリスクの程度に応じ補償する場合には、研究者等の意思・判断として、その内容や程度について被験者に対しあらかじめ文書により具体的に説明するとともに、文書により同意を得ておく必要がある。

（４）研究者等は、被験者が経済上又は医学上の理由等により不利な立場にある場合には、特に当該被験者の自由意思の確保に十分配慮しなければならない。

（５）研究者等は、被験者に対し、当該被験者が与えたインフォームド・コンセントについて、いつでも不利益を受けることなく撤回する権利を有することを説明しなければならない。

＜細則＞

研究者等は、被験者に対し、インフォームド・コンセントの撤回にあっては、文書で行うよう説明することが望ましい。

２　代諾者等からインフォームド・コンセントを受ける手続

＜細則＞

１．代諾者等からインフォームド・コンセントを受けることができる場合及びその取扱いについては、以下のとおりとし、いずれの場合も、研究責任者は、当該臨床研究の重要性、被験者の当該臨床研究への参加が当該臨床研究を実施するにあたり必要不可欠な理由及び代諾者等の選定方針を臨床研究計画書に記載し、当該臨床研究計画書について倫理審査委員会による承認及び臨床研究機関の長による許可を受けなければならない。

イ　被験者が疾病等何らかの理由により有効なインフォームド・コンセントを与えることができないと客観的に判断される場合

ロ　被験者が未成年者の場合。ただし、この場合においても、研究者等は、被験者にわかりやすい言葉で十分な説明を行い、理解が得られるよう努めなければならない。また、被験者が 16 歳以上の未成年者である場合には、代諾者等とともに、被験者からのインフォームド・コンセントも受けなければならない。

【被験者が生存している段階にインフォームド・コンセントを受けることができない場合】

ハ　被験者の生前における明示的な意思に反していない場合

２．研究責任者は、一般的には、被験者の家族構成や置かれている状況等を勘案して、以下に定める者の中から被験者の意思及び利益を代弁できると考えられる者を選定することを基本とし、臨床研究計画書に代諾者等の選定方針を記載しなければならない。

なお、被験者の家族構成や置かれている状況等とは、被験者と代諾者等の生活の実質や精神的共同関係からみて、被験者の最善の利益を図ることが可能な状況をいうものである。

イ　当該被験者の法定代理人であって、被験者の意思及び利益を代弁できると考えられる者

ロ　被験者の配偶者、成人の子、父母、成人の兄弟姉妹若しくは孫、祖父母、同居の親族又はそれらの近親者に準ずると考えられる者

３．研究責任者は、一般的には、死亡した被験者の家族構成や置かれていた状況、慣習等を勘案して、以下に定める者の中から被験者の生前の意思を代弁できると考えられる者を代諾者として選定することを基本とし、臨床研究計画書に代諾者等の選定方針を記載しなければならない。

イ　死亡した被験者の配偶者、成人の子、父母、成人の兄弟姉妹若しくは孫、祖父母、同居の親族又はそれらの近親者に準ずると考えられる者

（１）研究者等は、被験者からインフォームド・コンセントを受けることが困難な場合には、当該被験者について臨床研究を実施することが必要不可欠であることについて、倫理審査委員会の承認を得て、臨床研究機関の長の許可を受けたときに限り、代諾者等からインフォームド・コンセントを受けることができる。

（２）研究者等は、未成年者その他の行為能力がないとみられる被験者が臨床研究への参加についての決定を理解できる場合には、代諾者等からインフォームド・コンセントを受けるとともに、当該被験者の理解を得なければならない。

参考資料３－３

薬食審査発 1024 第１号
平成２３年１０月２４日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長

「医薬品の臨床試験の実施の基準に関する省令」の運用について

医薬品の臨床試験の実施の基準に関する省令（平成９年厚生省令第 28 号。以下「ＧＣＰ省令」という。）の運用については、「医薬品の臨床試験の実施の基準の運用について」（平成２０年１０月１日付け薬食審査発第 1001001 号厚生労働省医薬食品局審査管理課長通知。以下「旧運用通知」という。）によりお示ししてきたところです。

今般、治験の効率的な実施のため、ＧＣＰ省令の運用を別添のとおり改訂しましたので、貴管下関係業者、医療機関等に対し周知いただきますよう御配慮願います。

なお、この通知は、平成２４年４月１日から施行し、施行に伴い、旧運用通知は廃止いたします。

また、この通知日以降に行われる医薬品の臨床試験については、この通知の規定を適用しても差し支えありません。

（被験者の意思に影響を与える情報が得られた場合）
第 54 条　治験責任医師等は、治験に継続して参加するかどうかについて被験者の意思に影響を与えるものと認める情報を入手した場合には、直ちに当該情報を被験者に提供し、これを文書により記録するとともに、被験者が治験に継続して参加するかどうかを確認しなければならない。この場合においては、第 50 条第５項及び第 52 条第２項の規定を準用する。
２　治験責任医師は、前項の場合において、説明文書を改訂する必要があると認めたときは、速やかに説明文書を改訂しなければならない。
３　治験責任医師は、前項の規定により説明文書を改訂したときは、その旨を実施医療機関の長に報告するとともに、治験の参加の継続について改めて被験者の同意を得なければならない。この場合においては、第 51 条から前条までの規定を準用する。

〈第１項〉

１　治験への参加の継続について被験者又は代諾者の意思に影響を与える可能性のある情報が得られた場合には、治験責任医師又は治験分担医師は、当該情報を速やかに被験者又は代諾者に伝え、被験者の治験への参加の継続について、被験者又は代諾者の意思を確認すること。この場合にあっては、当該情報を被験者又は代諾者に伝えたことを文書に記録しておくこと。

２　第 50 条第５項（質問する機会を与え、かつ質問に十分に答えること。）、第 52 条第２項（治験への参加の継続に関し、強制したり又は不当な影響を及ぼさないこと。）を準用する。

〈第２項〉〈第３項〉

１　被験者の同意に関連し得る新たな重要な情報が得られた場合には、治験責任医師は、速やかに当該情報に基づき説明文書を改訂し、予め治験審査委員会の承認を得ること。また、治験責任医師又は治験分担医師は、すでに治験に参加している被験者に対して、当該情報を被験者又は代諾者に速やかに伝え、治験に継続して参加するか否かについて、被験者又は代諾者の意思を確認するとともに、改訂された説明文書を用いて改めて説明し、治験への参加の継続について被験者又は代諾者から自由意思による同意を文書により得ること。

（緊急状況下における救命的治験）
第 55 条　治験責任医師等は、第７条第３項又は第 15 条の４第３項に規定する治験においては、次の各号のすべてに該当する場合に限り、被験者となるべき者及び代諾者となるべき者の同意を得ずに当該被験者となるべき者を治験に参加させることができる。
１）被験者となるべき者に緊急かつ明白な生命の危険が生じていること。
２）現在における治療方法では十分な効果が期待できないこと。
３）被験薬の使用により被験者となるべき者の生命の危険が回避できる可能性が十分にあると認められること。
４）予測される被験者に対する不利益が必要な最小限度のものであること。
５）代諾者となるべき者と直ちに連絡を取ることができないこと。

2　治験責任医師等は、前項に規定する場合には、速やかに被験者又は代諾者となるべき者に対して当該治験に関する事項について適切な説明を行い、当該治験への参加について文書により同意を得なければならない。

〈第１項〉〈第２項〉

1　緊急状況下における救命的な内容の治験であって、被験者となるべき者から事前の同意を得ることが不可能である場合においては、被験者となるべき者の代諾者からその同意を得るべきである。被験者となるべき者の事前の同意が不可能で、かつ、被験者となるべき者の代諾者と連絡が取れない場合には、次の各号の全てに該当する場合に限り治験に参加させることができる。

（１）被験者となるべき者に緊急かつ明白な生命の危険が生じていること。

（２）現在利用可能な治療方法では十分な効果が期待できないこと。

（３）被験薬の使用により被験者となるべき者の生命の危険が回避できる可能性が十分にあると認められること。

（４）予測される被験者に対する不利益が最少限度のものであること。

（５）代諾者となるべき者と直ちに連絡をとることができないこと。

2　治験責任医師等は、あらかじめ、治験審査委員会の承認文書に被験者及び代諾者の同意なしに治験に加わった者の人権の保護、安全の保持及び福祉の向上を図る方法が明記されていることを確認しておくこと。

3　第２項の趣旨から、被験者の身元が明らかでない者を治験の対象としないこと。

4　このような場合でも、被験者（又はその代諾者となるべき者）に対し、できるだけ速やかに当該治験に関する説明を行い、治験の継続及びその他の適切な事項について文書により同意を得ること。また、その経過と結果を治験審査委員会に報告すること。

参考資料３－４

「超急性期軽度低体温療法による重症脳障害患者の予後改善戦略と医療費評価」多施設無作為対照臨床研究

主任研究者
前川剛志　　山口大学医学部教授　生体侵襲医学講座

研究要旨

急性重症脳障害、特に頭部外傷患者で受傷後超急性期（３～６時間以内）に体温の上昇を抑制し、軽度低体温（32～34℃）療法を開始すれば、患者の予後が著明に改善される可能性が高い。これを多施設・無作為・対照・臨床研究（RCT）で実施し、新しい医療技術を開発して国民の保健に資するとともに、その成果を世界に向けて発信することを目的とする。

重症頭部外傷の予後は悪く、従来の治療法では限界があり、予後を著明に改善する治療法の開発が急務である。軽度低体温療法が有効なことは基礎（動物）実験で証明されており、臨床への応用が始まっているが、実験動物と人間の違いを配慮した治療法の検討がなされておらず、新たなプロトコールでEBMに基づく有効な治療法を確立する必要がある。本研究グループは救急医療の最前線で診療しており、軽度低体温療法開始の時間限界である受傷後６時間以内をクリアできる。我々の事前研究では本療法により良好な結果が得られており、患者および家族の益するところは大きい。また、本治療法は初期には集中治療の必要性等により医療費が高額となるが、長期的・総合的に従来の治療法と比較すれば、本治療法の方が安くなる可能性もあるので、本研究で費用効果効率も検討する。

各参加施設におけるバラツキをなくして良質のデータを得るために、徹底した全身管理（人工呼吸、スワン・ガンツカテーテルによる循環管理、頭蓋内圧測定など）を含む本治療法の統一化を図り、本年度は 100 症例を目標にデータを集積する。２年目には150症例を、３年目には50症例を集め、データの解析と報告を行う。

1．緒言

急性重症脳障害、特に頭部外傷患者で受傷後超急性期（３～６時間以内）に体温上昇を抑制すれば、患者の予後が著明に改善される可能性が高い。さらに、正常体温以下にまで体温を下げる治療法である軽度低体温（32～34℃）療法を開始すれば、更なる効果が期待できる。これを多施設・無作為・対照・臨床研究（RCT）で実施し、新しい医療技術を開発して国民の保健に資するとともに、その成果を世界に向けて発信することが重要である。

頭部外傷、くも膜下出血、脳内出血、脳梗塞などの重症脳障害の予後は悪く、従来の治療法では限界があり、予後を著明に改善する治療法の開発が急務である。軽度低体温療法の有効性については基礎（動物）実験で証明されており、臨床への応用が始まっているが、実験動物と人間の違いを配慮した治療法の検討がなされておらず、新たなプロトコールでEBMに基づく有効な治療法を確立する必要がある。本研究グループは救急医療の最前線で診療しており、軽度低体温療法開始の時間限界である受傷後６時間以内をクリアできる。我々の事前研究では本療法により良好な結果が得られており、QOLを高めて社会復帰した症例も多く、患者および家族の益するところは大きい。また、本治療法は初期には集中治療の必要性等により医療費が高額となるが、長期的・総合的に従来の治療法と比較すれば本治療法の方が安くなり、費用効果効率も優れているとの研究報告もある。

また、本治療法をEBMとして確立して諸外国に発信できれば、日本の臨床研究の評価も得られ、今後創薬等でも日本のデータの信頼性が高まり、益することが多いと思われる。

本年度は各参加施設でのバラツキをなくすために、徹底したプロトコールの作成と診療現場での本治療法の統一化を図り、データを集積する。

2．目的

重症頭部外傷患者に対する軽度低体温療法(脳低温療法)の有用性と適正な患者管理方法について、積極的に体温上昇を抑制する軽微低体温療法を対照として多施設無作為対照臨床研究（RCT）で検証する。また本治療法の医療経済上の利点を検証する。

3．対象

重症頭部外傷患者（グラスゴー・コーマ・スケール、４≦GCS≦8）

A．選択基準

（１）重症頭部外傷症例で、初診時のグラスゴー・コーマ・スケール、４≦GCS≦8の患者。但しＭ６の場合は除く（受傷後５時間以内にこの適応となった場合も含む。）

（2）受傷時刻が特定可能で 6 時間以内に軽度低体温療法（32.0～34.0℃）あるいは軽微低体温療法（35.5～37.0℃）が可能な患者。（軽度低体温群では 6 時間以内に 35.5℃まで体温を下げることを必要条件とする。）
（3）年齢 15 歳以上、70 歳未満。
（4）性別は問わない。
（5）家族または代諾者から文書による同意取得が可能な患者、または“Waiver of consent policy”を満たす患者。

（注）本臨床研究における“Waiver of consent policy”とは。

救命救急患者で本人の意識レベルが悪く、また家族等の代諾者と連絡が取れないためにインフォームド・コンセントが得られないが、この RCT の適応基準を満たす場合を言う。その後代諾者と連絡が取れた時点でインフォームド・コンセントが得られれば本研究を続行し、得られなければその時点で中止する。本研究では、重症頭部外傷の際に有害とされる高体温を早期から積極的に抑制することが前提であるため、患者にとって不利益を生じない点から“Waiver of consent policy”が採用できる。

B．除外基準

1）全身性のもの
（1）出血性ショックなど、他部位の損傷により収縮期血圧が 90mmHg 以上に保てない場合。
（2）導入前の血小板数が 50,000/mm^3 未満の場合。
（3）軽度低体温療法に耐えられないと判断される重篤な肝疾患を持つ患者。
（4）軽度低体温療法に耐えられないと判断される重篤な心不全を持つ患者。
（5）軽度低体温療法に耐えられないと判断される重篤な不整脈を持つ患者。
（6）急性心筋梗塞の所見がある患者。
（7）妊娠または妊娠の疑いがある患者。
（8）泥酔状態にある患者。

2）頭部外傷に関連するもの
（9）開放性脳損傷（重症例）患者
(10) 急性硬膜外血腫等で手術により予後良好と予測できる患者

3）その他
(11) 家族または代諾者が本研究への参加を拒否した場合。
(12) その他、主治医が不適格と判断した患者。

C．来院時低体温症例の扱い
（1）30.0℃（深部温）未満の症例は除外する。
（2）30.0℃以上の症例は pre-registration を行う。
35.5℃を目標に復温を開始し、インフォームドコンセントを得る。
（3）Registration 後、軽度低体温群に割り振られれば可及的に管理指針に従って 32.0～34.0℃に維持する。
（4）対照軽微低体温群に割り振ら れれば可及的に管理指針に従って 35.5～37.0℃に復温し、維持する。

4．臨床研究デザイン

多施設、無作為、対照、臨床研究（RCT）とする。

5．症例の登録および割付け

登録・ランダム化は、UMIN（大学病院医療情報ネットワーク）のインターネット医学研究データセンターのバックアップを受けて、24 時間体制のオンラインで行う。選択基準を満たし、除外基準のいずれにも該当しない対象候補患者が入院した場合、直ちに患者の性別、年齢、GCS をもって pre-registration を行う。UMIN より仮の症例登録番号が配布される。その後、高体温をきたさないよう積極的に体温管理しながらインフォームドコンセントを得る努力をする。インフォームドコンセントが得られた時点で registration を行う。受傷後２時間以内に家族または代諾者と連絡がとれなかった場合には waiver of consent policy を採用し、registration を行う。治療群の割付けは、対象例をランダムに年齢、施設、重症度(GCS)、性別に関して最小化法で２群の平衡をとりながら行う。対象の割付けは同一の麻酔方法のもとに以下の２群とする。

1）Primary Research; 背景麻酔をミダゾラム・非麻薬性鎮痛薬（M 群）で以下の２群に分類する。

・ 対照軽微低体温M群（50例）

高体温を防ぐとともに最低72時間は軽微低体温～常温（血液温35.5～37.0℃）とし、以後も極力常温を維持する。

・ 軽度低体温M群（100例）

最低72時間は体温を軽度低体温（血液温32.0～34.0℃）とし、その後極力常温を維持する。

2）Secondary Research;

（1）Primary Researchの検討で２群間に有意差が得られなかった場合。

・ 対照軽微低体温NLA群（50例）：

高体温を防ぐとともに最低72時間は軽微低体温～常温（血液温35.5～37.0℃）とし、以後も極力常温を維持する。

・ 軽度低体温NLA群（100例）：

最低72時間は軽度低体温（血液温32.0～34.0℃）とし、その後極力常温を維持する。

（2）Primary Researchの検討で２群間に有意差が得られた場合。

背景麻酔をM群（75例）とNLA群（75例）の2群とし、効果が認められた群の体温管理下に維持する。

超急性期重症脳障害患者に対する軽度低体温療法の評価に関する全国共同研究の説明

～waiver of consent に関する説明～

1. 当院では質の高い種々の医療を患者様に提供し、加えて、病気の治療法の効果についての検討も行っています。
2. 今回、ご家族が緊急入院されました。直ちに行った頭部の断層撮影検査（ＣＴ）で、重症の頭部外傷である事が判明いたしました。
3. 脳が損傷を受けますと、重症の場合には損傷を受けた部分だけでなく、健康であった部分にも影響が及び、脳全体がだめになってしまうことがあります。重症の場合には通常、体温が上昇し40℃を越えることもあります。そうなりますと、生命に危険性がおよぶとともに、助かったとしても麻痺や言葉の障害、意識がもどらないなどの後遺症が残ります。そのため、体温の異常な上昇を防ぐことが非常に大切です。
4. しかしながら、重症の頭部外傷の場合、現時点では、脳全体を回復させる完璧な治療法はありません。
5. 頭部外傷を負ってから数時間以内であれば、脳の温度を 32.0～34.0℃ぐらいまで少し下げることで、脳全体を保護できるということがわかってきました。これを「軽度低体温療法」または「脳低温療法」と呼んでおり、脳の障害を阻止して、麻痺や言葉の障害、意識がもどらないなどの後遺症を残さないようにするための新しい治療法として注目されています。
6. しかし、この治療法によって劇的に状態が改善し社会復帰できる例がある反面、体温を下げることによる全身への悪影響により、むしろ症状が悪化したり死亡する場合があることもわかっています。

7. 現在のところ、重症頭部外傷の場合この軽度低体温療法（32.0～34.0℃）が軽微な低体温（35.5～37.0℃）で治療する方法と比較して有効であるとする科学的根拠がありません。
8. そこで日本の主要病院が参加して「32.0～34.0℃の軽度低体温療法」と「35.5～37.0℃の軽微低体温療法」を比較して、いずれが安全で有効なものであるかを科学的に明らかにする研究を行っています。
9. これらの研究・治療は本来ならばご家族への十分な説明の上で、同意書に署名をいただいてから開始するべきですが、一刻も早くいずれかの治療法を開始することが患者様のために必要であったため、ご家族の到着を待たずして既に治療を開始しています。この判断を「waiver of consent」とよび、どちらの治療法でも治療・研究が患者様には有害でなく、治療効果が期待できる場合に採用される考え方です。
10. 患者様は無作為に以下のどちらかの治療方針に振り分けられています。
    1）32.0～34.0℃の「軽度低体温療法」を実施した上で、現在行い得る最良の医療を行う。
    2）35.5～37.0℃の「軽微低体温療法」を実施した上で、現在行い得る最良の医療を行う。
11. 前述のとおり、重症頭部外傷では通常でも 37.5～40.0℃以上に体温が上昇します。最近、外国の脳卒中に関する報告で体温が上昇した場合には予後が悪かったと言われています。ですから、この研究ではいずれに割り当てられても、厳重な体温管理を行い、体温上昇を防ぐことを前提としています。

12. この研究に参加して治療を継続されるかどうかはご家族の自由です。同意されない場合でも今後の治療において不利益を受けることはありません。また同意されてもその同意はいつでも撤回することができます。

平成　　年　　月　　日

説明医師名＿＿＿＿＿＿＿＿＿＿＿＿＿＿

所　　属＿＿＿＿＿＿＿＿＿＿＿＿＿＿

平成 14 年度厚生労働科学研究費補助金（医療技術評価総合研究事業）

「超急性期軽度低体温療法による重症脳障害患者の予後改善戦略と医療費評価」

主任研究者：山口大学救急医学講座　前川剛志

同意書

＿＿＿＿＿＿＿病院　病院長
＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿殿

患者氏名＿＿＿＿＿＿＿＿＿＿＿＿
（　　）歳

この度上記の者が、貴院の治療計画に従い、超急性期軽度低体温療法の効果に関する臨床研究に参加するにあたり、その必要性、内容、合併症および副作用等について、詳細な説明を受け了承しましたのでその実施を承諾します。尚、参加はあくまでも自由意志に基づくものであり、同意しない場合でもこれにより不利益を受けないこと、いつでも自由意志によって同意を撤回できることを確認の上、この同意書に署名、捺印します。

平成　　年　　月　　日

家族・代諾者氏名＿＿＿＿＿＿＿＿＿＿＿＿印　続柄（　　）

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

上記患者に対する治療については、私が説明し了解されたことを確認しました。

平成　　年　　月　　日

医師名＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿印

参考資料3－5

SAVE-J 資料 3　(2010年4月5日改訂)

委員会記載　資料番号＿＿＿＿＿＿＿＿

帝京大学医学部倫理委員会申請書

平成22年　3月　16日

倫理審査委員会委員長殿

帝京大学医学部附属病院
救命救急センター教授　　坂本哲也　　印

下記の案件につき倫理審査を申請します。

1. 研究・教育課題名：心肺停止患者に対する心肺補助装置等を用いた高度救命処置の効果と費用に関する多施設共同研究

2. 審査の対象：
１）臨床研究（前向き研究）；■その他（研究期間の延長と課題名変更等）

3. 研究・教育の概要（目的、方法）：
目的：経皮的心肺補助装置(以下 PCPS)の適応となる来院時心肺停止症例に対して、PCPS を利用した心肺蘇生がアウトカムを改善することを比較対照試験によって検討する。
方法:前向き観察研究（非ランダム化比較対照試験）

4. 対象およびその目標人数：
全施設（目標 50 施設）で PCPS 群 120 例、非 PCPS 群 240 例を予定。当救命救急センターでは、PCPS 群 15 例の登録を予定している。

5. 研究・教育の学術的意義と社会的意義：
来院時心肺停止症例に対する PCPS の有用性、安全性、経済性が明確にされる。

6. 研究・教育の実施責任者：
坂本哲也（帝京大学医学部附属病院　救命救急センター　教授）

7. 研究・教育の期間：
本学および研究参加施設の倫理審査委員会の承認後から平成 24 年 3 月 31 日まで。

8. 研究・教育の場所：
帝京大学医学部附属病院　救命救急センター

9. 研究における主な倫理的配慮：

本研究は観察研究なので疫学研究に関する倫理指針における観察研究の記載に従う。具体的にはデータ提供に対する同意を患者もしくはその家族から個別に取得するのではなく、ポスター等により、研究実施の情報公開とデータ利用を拒否する機会を提供することを原則とする。ただし、PCPS 使用群については、本研究の主たる研究対象であることを鑑みて、個別に説明を行い、データ提供の同意文書を得ることとする。データ提供の同意文書は、PCPS による治療が開始された後、患者登録を行う時点で取得する。

本研究では、原則としてそれぞれの参加医療機関が通常行っている治療方針に基づいて PCPS の使用が決定されるので、PCPS の使用に関する説明と同意についても参加施設が通常 PCPS 使用時に行っている方法に準ずるものとする。ただし、一般に心肺停止治療中という状況の厳しい時間的制約の中で、PCPS の使用に関する説明を十分に行い、同意を得ることは現実的には不可能である場合が多く、患者の利益を最大限に考慮した上で PCPS の導入後に家族への説明が行われているのが実態である。従って、本研究では PCPS の使用に関して文章による事前の同意は必要としない。

なお、各参加医療機関における同意取得の方法に関しての最終判断は、それぞれの医療機関の倫理委員会の判断に委ねる。

患者データは連結可能匿名化し、資料は、試験責任医師が各施設内の施錠可能な保管庫で管理し、研究発表 5 年後に裁断処理を行う。電子ファイルはパスワードをかけて保管し、データ送信時には暗号化通信、または親展で郵送する。

また、研究の内容・効果・安全性について、定期的に、独立した「外部効果・安全モニタリング委員会」に報告する。

10. 研究によって生ずる可能性のある個人の利益、不利益・障害事象とその対応：

本研究は、原則、各医療機関が通常行っている治療の結果に基づく観察研究であるため、個人の利益、不利益は発生しない。

本研究のプロトコルに沿った治療による有害事象（出血、血栓・塞栓、虚血、感染、PCPS 施行に由来する死亡）が発生した場合、直ちにプロトコルに沿った治療を中止し適切な処置を行う。また試験責任医師は、カルテならびに症例報告書に経過等を記載し、有効性・安全性の評価を行う。研究責任者は倫理委員会に対する報告を行う。

個人情報漏洩が起こった場合、研究責任者ならびに試験責任医師は、患者・家族等に文書または必要に応じ電話で報告する。研究責任者は、研究機関の長への報告も行う。

11. 患者の経済的負担または患者への支払いの有無：なし

12. 研究の中止の条件とその対応および報告の方針：

試験責任医師は、下記の理由等で治療プロトコルによる治療が困難と判断した場合、本研究を中止する。

1. プロトコルに関する安全性，有効性に関する重大な情報が得られたとき。
2. 患者の登録・参加が困難で，予定患者を達成することが困難と判断されたとき。
3. 予定患者数または予定期間に達する前に，中間解析等により試験の目的が達成されたとき。
4. 治験審査委員会（IRB）により，試験実施計画等の変更の指示があり，これを受入れることが困難と判断されたとき。

※　各患者のデータ使用を中止する条件

a)　患者あるいは代諾者からデータ提供をとりやめる連絡があった場合

b)　本研究の適格規準に患者が合致しないと医師が判断した場合

中止の場合、試験責任医師または試験分担医師は、プロトコルに沿った治療を中止し、適切な処置を行う。またカルテに、中止の経過を記載し、有効性・安全性の評価を行う。また、データマネジメントセンターに対する報告を行う。

13. 研究成果の取りまとめとその扱い：

個人を特定できない形にした上で、研究終了後 5 年以内に、学会、論文発表を行う。

14. 研究資金源と主要支出：　□研究費 A　□研究費 B　□研究費 C　■その他

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）心肺停止患者に対する心肺蘇生補助装置等を用いた高度救命処置の効果と費用に関する多施設共同研究）

厚生労働科学研究費補助金（循環器疾患/糖尿病等生活習慣病対策総合研究事業）心肺停止患者に対する心肺蘇生補助装置等を用いた高度救命処置の効果と費用に関するエビデンスを構築するための多施設共同研究）（22111001）

；主要支出（データマネジメントセンター委託費、会議費等。なお本研究において診療行為に対する支出はない。）

15. 倫理委員会への中間および最終報告の方針：

実施状況、倫理的配慮の状況、不利益・障害事象の発生状況などについて開始 1 年後、終了時に中間報告書および最終報告書を倫理委員会に提出する。

16. 添付資料一覧：

説明文書

同意文書

研究へのデータ提供者への説明文書

「心肺停止患者に対する心肺補助装置等を用いた高度救命処置の効果と費用に関する多施設共同研究」に＿＿＿＿＿＿＿＿様の診療記録のデータを使用させていただきたく、その内容を説明いたします。

この研究について、十分な説明をいたしますので、よく理解された上で、あなたのご判断で、この研究のための＿＿＿＿＿＿＿＿様の診療記録のデータを使わせていただけるかどうかを決めてください。

いったんご提供を承諾いただいた後でも、いつでもとりやめることができます。わからないことはいつでも質問してください。

1　研究の目的・意義

この研究は、心臓と肺が止まった患者さんに、人工心肺の機械(心臓と肺の役割を助ける機械)を使って治療したことが、患者さんによい結果をもたらしたかを調べることを目的としています。

2　研究へのデータ提供の自由

この研究では、診療記録のデータを分析させていただきます。データを提供するかしないかは、あなたの自由な意思で決めてください。ご提供いただけない場合でも、治療などへの影響は一切ありません。

3　研究へのデータ提供をとりやめる自由

この研究へのデータ提供を承諾いただいた後でも、いつでもご提供をとりやめることができます。

4　研究へのデータ提供をお願いする理由

患者さんご本人による同意が困難な場合、代理人の方からの同意を頂くことでデータを提供していただくことも可能です。これまで、人工心肺をつかった治療の有効性は、日本でも、海外でも、十分に解明されていません。この研究の結果が、救急医療の質を高めることにつながることが期待されているため、一人でも多くの患者さんにご提供いただけるよう、ご協力をお願いしています。

5　研究の方法

人工心肺の機械を使う病院で治療を受けた患者さんと、使わない病院で治療を受けた患者さん、両方のデータを集めて、退院するときの健康状態を比べます。

6　研究で集めるデータ

患者さんの性別、年齢、身長、体重、受けた治療の内容、検査の結果、退院するときの健康状態、退院した後の健康状態など、主に患者さんの診療記録に書かれたデータを集めます。

7　データを使う目的

集めたデータは、この研究のためだけに使います。他の目的で使うことは一切ありません。

8　データの扱い

患者さんのデータは、すべて、お名前など個人が特定できる情報を含まない形にして（匿名化）扱います。患者さんのデータが入ったすべての文書や電子媒体は、医師が責任をもって、鍵のかかるところに厳重に保管します。この研究が終わったら、すべての文書や電子媒体を廃棄します。

9　研究の結果の扱い

研究の成果は、患者さんのお名前など、患者さん個人が特定できる情報を一切含まない形にして、学会や論文で発表します。

10　この研究にデータを提供することによって予想される利益

この研究にデータを提供することによって、直接、患者さんに利益になることはありませんが、この研究によって、将来、同じような病気で心臓が止まった他の患者さんの役に立つ情報が得られることが期待されています。

11　この研究にデータを提供することによって予想される害と、その場合の対応

個人情報の保護に十分注意した上で、患者さんのデータを集めますので、データ提供による害はないと考えられます。万が一、個人情報がもれるような事故が発生した場合には、速やかにご報告し、原因を調べて必要な対応を行います。

12 研究組織

この研究は、本施設を含む全国の救命救急センターや循環器科を中心に行われます。データの管理や集計などは、NPO 法人のヘルスサービス R&D センターが担当しています。

13 研究の責任施設

この研究の責任施設は帝京大学医学部附属病院　救命救急センターです。

14 研究の期間

この研究は、平成 24 年 3 月 31 日までの期間で行われる予定です。

15 研究の資金源

この研究は、厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）で行われています。

16 データ提供者の負担の有無

この研究にデータを提供していただくのに費用をご負担いただくことはございません。

17 データの使用を中止する条件とその場合の対応

以下のような場合には、研究全体を中止します。

- 患者さん、あるいは代理の方から、研究へのデータ提供をとりやめる連絡があった場合
- 医師が、患者さんがこの研究にデータ提供いただける条件を満たしていないと判断した場合

18 この研究に関する問い合わせや、研究へのデータ提供をとりやめる場合のご連絡方法について

この研究に関する問い合わせや、研究へのデータ提供をとりやめる場合には、下記にご連絡ください。

【連絡先】SAVE-J 事務局（帝京大学医学部附属病院　救命救急センター内）
電話番号：03-3964-2898

説明日：　　年　　月　　日
説明者：　　科

参考資料３－６

平成25年度 厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

実証研究の実施を通じて得られた

救急の現場における臨床研究でのインフォームド・コンセントの課題について

平成25年度厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班
主任研究者　野口　宏
倫理問題担当
分担研究者　横田裕行

１．はじめに

厚生労働科学研究「救急救命士の処置範囲に係る実証研究」研究班は、平成24年7月より、救急救命処置に関する臨床研究（介入研究）を実施した。研究の実施にあたっては、研究の適切性について評価を依頼した日本救急医学会からの指摘と、厚生労働省の定める「臨床研究に関する倫理指針」を踏まえて、その処置の対象者からインフォームド・コンセントを文書で受ける手続きをとることを原則とした。しかしながら、この手続きについては、救急の現場で行われた経験がこれまでになく、その実施にあたっていくつかの困難や課題があった。

本報告では、実証研究の実施を通じて得られた、救急の現場における臨床研究でのインフォームド・コンセントの課題について述べる。

２．実証研究の概要

・救急の現場で、救急救命士が傷病者に対して行う、救急救命処置（ア 血糖測定と低血糖発作症例へのブドウ糖溶液の投与、イ 重症喘息に対するβ刺激薬の使用、ウ 心肺機能停止前の静脈路確保と輸液）の効果等を検証する介入研究として実施した。

・全国の39の地域、126の消防本部、2,332人の救急救命士が参加した大規模実証研究である。

・救急の現場での初めての介入試験（historical control study）となった。（＊研究班調べ）

３．インフォームド・コンセントを文書で受ける手続きの概要

①処置の実施前に救急救命士が傷病者本人に説明し、傷病者からのインフォームド・コンセントを傷病者が署名した文章で受けることを原則とした。

②ただし、傷病の状態から、傷病者からのインフォームド・コンセントを受けることが困難な場合には、その代諾者に説明しインフォームド・コンセントを代諾者の署名した文書で受けることとした。

（①もしくは②による同意と署名が得られない場合は、処置の対象から除外した。）

③　②の場合において、傷病者本人の状態が回復した後に傷病者本人に説明し、傷病者からインフォームド・コンセントを文書で受けるように努めた。

＊「臨床研究に関する倫理指針」（厚生労働省　平成15年7月30日（平成16年12月28日全部改正、平成20年7月31日全部改正）に準拠

４．３．の手続きを決めるにあたって、議論となった事項と対応

① 救急の現場の傷病者の状況等について

・救急の現場、すなわち傷病者に生命の危険が切迫している状況においては、傷病者本人は、意識障害、循環不全等＊に陥っており、説明を適切に理解し判断できる状況ではない。（＊例えば、低血糖による意識障害や、ショック（循環不全）による脳循環障害による意識障害の傷病者など）

・たとえ、本人から同意書などに署名を得たとしても、このような状況で得た同意書の署名の、実質的な信頼性についての懸念が払拭できない。

（対応）傷病者が説明を適切に理解し判断できる状況にない場合は、代諾者に説明し、代諾者から署名を得ることとした。

② 救急の現場での代諾者の状況等について

・傷病者からの同意を得ることが困難な場合、家族などがその代諾者となり得るが、救急の現場に、そのような者が必ずしも居合わせているわけではない。居合わせていたとしても、その者が傷病者の適切な代諾者となり得るのか、救急の現場で短時間のうちに判断するのは困難である。

・たとえ、適切な代諾者が速やかに見つかったとしても、その者が、限られた時間のうちに状況を適切に判断し、同意書などに署名することは困難である。

・さらには、たとえ適切な代諾者から同意書などに署名を得たとしても、このような状況で得た同意書の署名の、実質的な信頼性についての懸念が払拭できない。

（対応）代諾者がいない場合は、対象から除外せざるを得なかった。代諾者がいた場合に、代諾者に簡潔、丁寧な説明が少しでも可能になるように、予め実証研究に参加する救急救命士に対して研修などを実施した。また、ポスター、ビラ、ホームページ等で地域住民に周知を行うなどした。しかしながら、代諾者の適性や、差し迫った状況で得た同意書の署名の、実質的な信頼性についての懸念は払拭できなかった。

③ 救急の現場での手続きに要する時間について

・そもそも、傷病者に生命の危険が切迫している状況においては、インフォームド・コンセントを受けることに時間を費やすこと自体が、傷病者の不利益となりえる。数十秒、数分という時間間隔で直ちに処置や投薬が必要な差し迫った状況においては、たとえ数分であっても、その手続に時間を要することが、そもそも倫理的ではない可能性がある。

（対応）生命の危険が切迫しており、同意を得るための手続きの最中にも心停止に至ることが懸念されるほどの状況においては、傷病者や代諾者には説明を行わず、今回の実証研究の対象から外すことにした。しかしながら、生命の危険から救命するための処置の効果を検証する実証研究であることとの矛盾が生じた。

5．実証研究での同意の取得の状況

・本人、代諾者から同意を得られなかった例　110/1625例、7%
　＊代諾者がいなかった事例、本人もしくは代諾者が不同意だった例を含む
・同意を得られた事例の内訳（サンプル調査：3協議会/19MC協議会）
　本人が署名した例　　5/100例、5%）
　代諾者が署名した例　95/100例、95%）

6．実証研究中に実際に生じた事例

インフォームド・コンセントを受ける手続きの最中や直後に、次の事例の発生があった。いずれも、事後検証においては同意の手続きや処置が直接の原因で心停止に至ったと判断された例はない。しかしながら、手続きに要した時間が傷病者に悪い影響を与えたと本人や家族に疑問をいだかせる可能性が残る。

・代諾者から同意を得ようと、書面の準備の最中に心停止に至った例（別添参照）
・実証研究や処置などについて、家族に説明の最中に傷病者の状態が急激に悪化し、後に心停止に至った例（別添参照）
・傷病者もしくは代諾者から書面での同意を得たあとから、処置を実施するまでの間に心停止に至った例　など

7．まとめ

救急の現場での臨床研究の実施には、インフォームド・コンセントの手続きに次の点で課題がある。

・傷病者に生命の危険が切迫している救急の現場においては、多くの場合、傷病者本人は意識障害などによりインフォームド・コンセントの対象となりえない。

・救急の現場においては、傷病者に代わる家族などが居合わせているとは限らない。いたとしても、差し迫った状況で、その者が適切な代諾者かどうか短時間で判断するのは困難である。

・傷病者本人もしくは代諾者から署名で同意を得たとしても、差し迫った状況下での説明と同意では、その同意の実質的な信頼性についての懸念が払拭できない。

・そもそも、救命のための処置を必要とする差し迫った状況においては、インフォームド・コンセントの手続きに時間を費やすこと自体が適切でない場合があり得る。

（別添参照）

インフォームド・コンセントを受ける手続きの最中や直後に心停止に陥った例

事案①

（日時）
平成24年●月●日（●）　16時●分　覚知

（概要）
80才代の女性、「嘔吐および悪心」を訴え、家族が救急要請した。
救急隊現場到着時、寝室に右側臥位でおり、意識レベルⅠ-1（見当識は保たれているが意識清明ではない）、橈骨動脈で脈拍を触れず、皮膚に冷感、湿潤ありショック状態であったため、「ショックの傷病者に対する心肺機能停止前の静脈路確保と輸液」の実証研究の対象と判断した。
バイタルサインを測定し、家族から同意を得ようと書類をとりだそうとしていたところで容体変化あり。心肺停止に移行した。直ちに心肺蘇生を開始し、AEDを装着、器具を用いた気道確保等を実施しながら、医療機関に搬送した。

事案②

（日時）
平成24年●月●日（●）　12時●分　覚知

（概要）
80才代の男性、「意識レベルの低下」の通報に対して出動した。
現場到着時、意識レベルJCSⅠ－3（自分の名前・生年月日が言えない）、顔面蒼白で冷汗あり。橈骨動脈で脈拍を触知できない状態であった。直ちに、救急車に収容し、心電図モニターを装着した。高度除脈を確認し、ショック状態であるため、「ショックの傷病者に対する心肺機能停止前の静脈路確保と輸液」の実証研究の対象と判断した。
処置について、家族に説明に入るも、途中で傷病者の意識レベルが悪化しJCSⅢ－100（刺激しても覚醒しない）となった。心肺停止に陥る可能性が高いと判断し、実証研究の説明は中断した。搬送先医療機関の決定と同時に、傷病者の心肺停止を確認した。心肺蘇生を実施しながら搬送し、医療機関に収容した。

参考資料3－6

平成25年度厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

救急の現場における臨床研究でのインフォームド・コンセントの課題について

平成25年度厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班
主任研究者　野口　宏
分担研究者（倫理問題担当）　横田裕行

平成25年度 厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

はじめに

- 平成24年7月より、救急救命処置に関する臨床研究（介入研究）を実施した。研究の実施に際し、その処置の対象者からインフォームド・コンセントを文書で受ける手続きをとることを原則*とした。

  ＊研究の適切性について評価を依頼した日本救急医学会からの指摘と、厚生労働省の定める「臨床研究に関する倫理指針」に基づいた。

- しかしながら、この手続きについては、救急の現場で行われた経験がこれまでになく、その実施にあたっていくつかの課題があった。

- 本報告では、実証研究の実施を通じて得られた、救急の現場における臨床研究でのインフォームド・コンセントの課題について述べる。

平成25年度 厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

実証研究の概要

- 救急の現場で、救急救命士が傷病者に対して行う、救急救命処置*の効果等を検証する介入研究として実施した。

  *①血糖測定と低血糖発作症例へのブドウ糖溶液の投与、②重症喘息に対する吸入β刺激薬の使用、③心肺機能停止前の静脈路確保と輸液

- 全国の39の地域、126の消防本部、2,332人の救急救命士が参加した大規模実証研究であった。

- 救急の現場での初めての介入試験（historical control study）となった。

平成25年度厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

インフォームド・コンセントを文書で受ける手続きの概要

①救急救命士が傷病者本人に説明し、傷病者からのインフォームド・コンセントを、処置の実施前に、傷病者が署名した文章で受けることを原則とした。

②ただし、傷病の状態から、傷病者本人からのインフォームド・コンセントを受けることが困難な場合には、その代諾者に説明し、インフォームド・コンセントを代諾者の署名した文書で受けることとした。

＊①もしくは②による同意と署名が得られない場合は、処置の対象から除外した。

＊②の場合において、傷病者本人の状態が回復した後に、傷病者本人に説明し、傷病者からインフォームド・コンセントを文書で受けるように努めた。

＊上記は、いずれも「臨床研究に関する倫理指針」（厚生労働省　平成15年7月30日（平成16年12月28日全部改正、平成20年7月31日全部改正）に準拠

平成25年度厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

課題①：傷病者の状況等について

- 救急の現場、すなわち生命の危険が切迫している状況においては、意識障害、循環不全等＊に陥っており、説明を適切に理解し判断できる状況ではない。

  （＊例えば、低血糖による意識障害や、ショック（循環不全）による脳循環障害による意識障害の傷病者など）

- たとえ、本人から同意書などに署名を得たとしても、このような状況で得た同意書の署名の、実質的な信頼性についての懸念が払拭できない。

（対応）

傷病者が説明を適切に理解し判断できる状況にない場合は、代諾者に説明し、代諾者から署名を得ることとした。

平成25年度 厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

課題②：代諾者の状況等について

- 救急の現場に、家族などの代諾者となり得る者が必ずしも居合わせているわけではない。
- いたとしても、その者が傷病者の適切な代諾者となり得るのか、短時間のうちに判断するのは困難である。
- たとえ、適切な代諾者が速やかに見つかったとしても、その者が、限られた時間のうちに状況を適切に判断し、同意書などに署名することは困難である。
- さらには、たとえ適切な代諾者から同意書などに署名を得たとしても、このような状況で得た同意書の署名の、実質的な信頼性についての懸念が払拭できない。

（対応）

・代諾者がいない場合は、対象から除外せざるを得なかった。

・代諾者がいた場合に、簡潔、丁寧な説明が少しでも可能になるように、予め実証研究に参加する救急救命士に対して研修などを実施した。また、ポスター、ビラ、ホームページ等で地域住民に周知を行うなどした。

・しかしながら、代諾者の適性や、差し迫った状況で得た同意書の署名の、実質的な信頼性についての懸念は払拭できなかった。

課題③：手続きに要する時間について

- そもそも、傷病者に生命の危険が切迫している状況においては、インフォームド・コンセントを受けることに時間を費やすこと自体が、傷病者の不利益となりえる。数十秒、数分という時間間隔で直ちに処置や投薬が必要な差し迫った状況においては、たとえ数分であっても、その手続に時間を要することが、そもそも倫理的ではない可能性がある。

（対応）

・生命の危険が切迫しており、同意を得るための手続きの最中にも心停止に至ることが懸念されるほどの状況においては、傷病者や代諾者には説明を行わず、今回の実証研究の対象から外すことにした。

・しかしながら、生命の危険から救命するための処置の効果を検証する実証研究であることとの矛盾が生じた。

平成25年度 厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

実証研究での同意の取得の状況

・本人、代諾者から同意を得られなかった例

110/1625例、7%

＊代諾者がいなかった事例、本人もしくは代諾者が不同意だった例など

・同意を得られた事例の内訳（サンプル調査：3協議会/19MC協議会）

本人が署名した例　5/100例、5%

代諾者が署名した例　95/100例、95%

実証研究中に生じた事例

手続きの最中や直後に、次の事例の発生があった。

- 代諾者から同意を得ようと、書面の準備の最中に心停止に至った例
- 実証研究や処置などについて、家族に説明の最中に傷病者の状態が急激に悪化し、後に心停止に至った例
- 傷病者もしくは代諾者から書面での同意を得たあとから、処置を実施するまでの間に心停止に至った例

いずれも、事後検証においては同意の手続きや処置が直接の原因で心停止に至ったと判断された例はないものの、手続きに要した時間が傷病者に悪い影響を与えたと、本人や家族に疑問をいだかせる可能性が残る。

平成25年度 厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

事例1

80才代の女性、「嘔吐および悪心」を訴え、家族が救急要請した。

救急隊現場到着時、寝室に右側臥位でおり、意識レベルⅠ-1（見当識は保たれているが意識清明ではない）、橈骨動脈で脈拍を触れず、皮膚に冷感、湿潤ありショック状態であったため、「ショックの傷病者に対する心肺機能停止前の静脈路確保と輸液」の実証研究の対象と判断した。

バイタルサインを測定し、家族から同意を得ようと書類をとりだそうとしていたところで容体変化あり。心肺停止に移行した。

直ちに心肺蘇生を開始し、AEDを装着、器具を用いた気道確保等を実施しながら、医療機関に搬送した。

平成25年度厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

事例2

80才代の男性、「意識レベルの低下」の通報に対して出動した。

現場到着時、意識レベルJCS Ⅰ －3（自分の名前・生年月日が言えない）、顔面蒼白で冷汗あり。橈骨動脈で脈拍を触知できない状態であった。直ちに、救急車に収容し、心電図モニターを装着した。高度除脈を確認し、ショック状態であるため、「ショックの傷病者に対する心肺機能停止前の静脈路確保と輸液」の実証研究の対象と判断した。

処置について、家族に説明に入るも、途中で傷病者の意識レベルが悪化しJCSⅢ－100（刺激しても覚醒しない）となった。心肺停止に陥る可能性が高いと判断し、実証研究の説明は中断した。搬送先医療機関の決定と同時に、傷病者の心肺停止を確認した。

心肺蘇生を実施しながら搬送し、医療機関に収容した。

平成25年度 厚生労働科学研究費補助金
「救急救命士の処置範囲に係る実証研究」研究班

まとめ

- 傷病者に生命の危険が切迫している救急の現場においては、多くの場合、傷病者本人は意識障害などによりインフォームド・コンセントの対象となりえない。
- 救急の現場においては、傷病者に代わる家族などが居合わせているとは限らない。いたとしても、差し迫った状況で、その者が適切な代諾者かどうか短時間で判断するのは困難である。
- 傷病者本人もしくは代諾者から署名で同意を得たとしても、差し迫った状況下での説明と同意では、その同意の実質的な信頼性についての懸念が払拭できない。
- そもそも、救命のための処置を必要とする差し迫った状況においては、インフォームド・コンセントの手続きに時間を費やすこと自体が適切でない場合があり得る。

参考資料3－7

The New England Journal of Medicine

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

ABSTRACT

Background Cardiac arrest with widespread cerebral ischemia frequently leads to severe neurologic impairment. We studied whether mild systemic hypothermia increases the rate of neurologic recovery after resuscitation from cardiac arrest due to ventricular fibrillation.

Methods In this multicenter trial with blinded assessment of the outcome, patients who had been resuscitated after cardiac arrest due to ventricular fibrillation were randomly assigned to undergo therapeutic hypothermia (target temperature, 32°C to 34°C, measured in the bladder) over a period of 24 hours or to receive standard treatment with normothermia. The primary end point was a favorable neurologic outcome within six months after cardiac arrest; secondary end points were mortality within six months and the rate of complications within seven days.

Results Seventy-five of the 136 patients in the hypothermia group for whom data were available (55 percent) had a favorable neurologic outcome (cerebral-performance category, 1 [good recovery] or 2 [moderate disability]), as compared with 54 of 137 (39 percent) in the normothermia group (risk ratio, 1.40; 95 percent confidence interval, 1.08 to 1.81). Mortality at six months was 41 percent in the hypothermia group (56 of 137 patients died), as compared with 55 percent in the normothermia group (76 of 138 patients; risk ratio, 0.74; 95 percent confidence interval, 0.58 to 0.95). The complication rate did not differ significantly between the two groups.

Conclusions In patients who have been successfully resuscitated after cardiac arrest due to ventricular fibrillation, therapeutic mild hypothermia increased the rate of a favorable neurologic outcome and reduced mortality. (N Engl J Med 2002;346:549-56.)

AN estimated 375,000 people in Europe undergo sudden cardiac arrest yearly.[1] Recovery without residual neurologic damage after cardiac arrest with global cerebral ischemia is rare. After cardiac arrest with no blood flow for more than five minutes, the generation of free radicals, together with other mediators, during reperfusion creates chemical cascades that result in cerebral injury.[2] Until recently, there was no therapy with documented efficacy in preventing brain damage after cardiac arrest.

Several studies have shown that moderate systemic hypothermia (30°C)[3] or mild hypothermia (34°C)[4-8] markedly mitigates brain damage after cardiac arrest in dogs. The exact mechanism for this cerebral resuscitative effect is not clear. A reduction in cerebral oxygen consumption[9,10] and other multifactorial chemical and physical mechanisms during and after ischemia have been postulated.[11-16] These include retardation of destructive enzymatic reactions, suppression of free-radical reactions, protection of the fluidity of lipoprotein membranes, reduction of the oxygen demand in low-flow regions, reduction of intracellular acidosis, and inhibition of the biosynthesis, release, and uptake of excitatory neurotransmitters.

Preliminary clinical studies have shown that patients treated with mild hypothermia after cardiac arrest have an improved neurologic outcome, without important side effects, as compared with the outcome in historical controls.[17-20]

We compared mild hypothermia with standard normothermia in patients who had had cardiac arrest due to ventricular fibrillation. The primary end point

Michael Holzer, M.D., Universitätsklinik für Notfallmedizin, Vienna, Austria, assumes overall responsibility for the integrity of the report. Address reprint requests to Dr. Fritz Sterz, Universitätsklinik für Notfallmedizin, Allgemeines Krankenhaus der Stadt Wien, Währinger Gürtel 18–20/6D, 1090 Vienna, Austria or at fritz.sterz@akh-wien.ac.at.

*The investigators who participated in the Hypothermia after Cardiac Arrest Study Group are listed in the Appendix.

was a favorable neurologic outcome within six months after cardiac arrest.[21-23] Secondary end points were mortality at six months and the incidence of complications during the first seven days. Nine centers in five European countries participated in the study.

METHODS

Patients

Patients seen consecutively in the emergency department in whom spontaneous circulation had been restored after cardiac arrest were eligible for the study. The criteria for inclusion were a witnessed cardiac arrest, ventricular fibrillation or nonperfusing ventricular tachycardia as the initial cardiac rhythm, a presumed cardiac origin of the arrest, an age of 18 to 75 years, an estimated interval of 5 to 15 minutes from the patient's collapse to the first attempt at resuscitation by emergency medical personnel, and an interval of no more than 60 minutes from collapse to restoration of spontaneous circulation.

Patients were excluded if they met any of the following criteria: a tympanic-membrane temperature below 30°C on admission, a comatose state before the cardiac arrest due to the administration of drugs that depress the central nervous system, pregnancy, response to verbal commands after the return of spontaneous circulation and before randomization, evidence of hypotension (mean arterial pressure, less than 60 mm Hg) for more than 30 minutes after the return of spontaneous circulation and before randomization, evidence of hypoxemia (arterial oxygen saturation, less than 85 percent) for more than 15 minutes after the return of spontaneous circulation and before randomization, a terminal illness that preceded the arrest, factors that made participation in follow-up unlikely, enrollment in another study, the occurrence of cardiac arrest after the arrival of emergency medical personnel, or a known preexisting coagulopathy.

Study Design

The study was designed as a randomized, controlled trial with blinded assessment of the outcome. The protocol and consent procedure were approved by the institutional review board of each participating center. For all patients, the requirement of informed consent was waived in accordance with the ethical standards of the local institutional review board and the guidelines for good clinical practice of the European Agency for the Evaluation of Medicinal Products.[24] The patient's family was informed about the trial, and the protocol specified that if there were any objections, the patient would be withdrawn from the study. However, there were no objections.

Treatment assignments were randomly generated by computer in blocks of 10, with stratification according to center. Sealed envelopes containing the treatment assignments were provided by the biostatistics center. Immediately after a patient had been enrolled, an envelope was opened, and the patient was assigned to the specified group.

Personnel involved in the care of patients during the first 48 hours after cardiac arrest could not be blinded with respect to treatment assignments. However, the physicians responsible for assessing the neurologic outcome within the first six months after the arrest were unaware of the treatment assignments.

Treatment

All patients received standard intensive care according to a detailed protocol. Sedation was induced by the intravenous administration of midazolam (0.125 mg per kilogram of body weight per hour initially) and fentanyl (0.002 mg per kilogram per hour initially), and the doses were adjusted as needed for 32 hours for the management of mechanical ventilation. To prevent shivering, paralysis was induced by the intravenous administration of pancuronium (0.1 mg per kilogram) every 2 hours for a total of 32 hours. Intracranial pressure was not monitored.

The temperature on admission was measured with an infrared tympanic thermometer (Ototemp LighTouch, Exergen, Watertown, Mass.). Further temperature measurements were made with a bladder-temperature probe (Foley catheter). Patients randomly assigned to the normothermia group were placed on a conventional hospital bed, and normothermia was maintained. Those randomly assigned to the hypothermia group were cooled to a target temperature of 32°C to 34°C with the use of an external cooling device (TheraKool, Kinetic Concepts, Wareham, United Kingdom). This device consists of a mattress with a cover that delivers cold air over the entire body. The goal was to reach the target bladder temperature within four hours after the return of spontaneous circulation. If this goal was not achieved, ice packs were applied. The temperature was maintained at 32°C to 34°C for 24 hours from the start of cooling, followed by passive rewarming, which we expected would occur over a period of 8 hours.

Data Collection

Data on cardiac arrest for individual patients were recorded in the Utstein style.[25] Laboratory tests were performed at base line, 12 and 48 hours after cardiac arrest, and as clinically indicated. Risk factors for an unfavorable outcome (hypotension or a nonfatal cardiac arrest after resuscitation) were documented.

Outcome

The primary outcome was a favorable neurologic outcome within six months, defined as a Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability) on a five-category scale; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).[21-23] The neurologic outcome was determined without knowledge of the patient's treatment assignment. Patients with good recovery or moderate disability had sufficient cerebral function to live independently and work at least part-time.

Secondary end points were overall mortality at six months and the rate of complications during the first seven days after cardiac arrest. Bleeding of any severity, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias, and pressure sores were recorded. Since an individual patient might have more than one complication at a time, the occurrence of at least one complication of any kind per patient was also documented.

Statistical Analysis

Continuous variables, which were not normally distributed, are reported as medians and interquartile ranges. Categorical variables are reported as counts and percentages. Primary and secondary outcomes were binary, and the chi-square test or Fisher's exact test, as appropriate, was used to compare outcomes in the hypothermia and normothermia groups. Trends across subgroups were measured with an extension of the Wilcoxon rank-sum test.[26] The difference in risk between the two groups, with the corresponding 95 percent confidence interval, was calculated as a measure of the absolute risk, which was then used to calculate the number needed to treat. Risk ratios are reported as a measure of relative risk.

We used a multivariate logistic-regression model to determine whether the association between the intervention and the primary and secondary outcomes (neurologic recovery and mortality) was confounded by base-line differences between the study groups. All the covariables listed in Table 1 were entered into the model, except for the dose of epinephrine, which was excluded because of collinearity with the interval from the patient's collapse to the restoration of spontaneous circulation. We converted odds ratios to risk ratios using the following formula:

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

STEPHEN A. BERNARD, M.B., B.S., TIMOTHY W. GRAY, M.B., B.S., MICHAEL D. BUIST, M.B., B.S., BRUCE M. JONES, M.B., B.S., WILLIAM SILVESTER, M.B., B.S., GEOFF GUTTERIDGE, M.B., B.S., AND KAREN SMITH, B.Sc.

ABSTRACT

Background Cardiac arrest outside the hospital is common and has a poor outcome. Studies in laboratory animals suggest that hypothermia induced shortly after the restoration of spontaneous circulation may improve neurologic outcome, but there have been no conclusive studies in humans. In a randomized, controlled trial, we compared the effects of moderate hypothermia and normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest.

Methods The study subjects were 77 patients who were randomly assigned to treatment with hypothermia (with the core body temperature reduced to 33°C within 2 hours after the return of spontaneous circulation and maintained at that temperature for 12 hours) or normothermia. The primary outcome measure was survival to hospital discharge with sufficiently good neurologic function to be discharged to home or to a rehabilitation facility.

Results The demographic characteristics of the patients were similar in the hypothermia and normothermia groups. Twenty-one of the 43 patients treated with hypothermia (49 percent) survived and had a good outcome — that is, they were discharged home or to a rehabilitation facility — as compared with 9 of the 34 treated with normothermia (26 percent, $P=0.046$). After adjustment for base-line differences in age and time from collapse to the return of spontaneous circulation, the odds ratio for a good outcome with hypothermia as compared with normothermia was 5.25 (95 percent confidence interval, 1.47 to 18.76; $P=0.011$). Hypothermia was associated with a lower cardiac index, higher systemic vascular resistance, and hyperglycemia. There was no difference in the frequency of adverse events.

Conclusions Our preliminary observations suggest that treatment with moderate hypothermia appears to improve outcomes in patients with coma after resuscitation from out-of-hospital cardiac arrest. (N Engl J Med 2002;346:557-63.)

CARDIAC arrest outside the hospital is a major cause of unexpected death in developed countries, with survival rates ranging from less than 5 percent to 35 percent.[1-3] In patients who are initially resuscitated, anoxic neurologic injury is an important cause of morbidity and mortality.[4]

Currently, the treatment of patients with coma after resuscitation from out-of-hospital cardiac arrest is largely supportive. Because cerebral ischemia may persist for some hours after resuscitation,[5] the use of induced hypothermia to decrease cerebral oxygen demand has been proposed as a treatment option.[6] Although this suggestion has been supported by studies in animal models,[7-12] the studies in humans that have been reported to date have been uncontrolled or retrospective.[13-18]

After a pilot study that suggested the feasibility, safety, and possible efficacy of this treatment,[16] we conducted a prospective, controlled trial comparing moderate induced hypothermia with normothermia in comatose survivors of out-of-hospital cardiac arrest.

METHODS

Study Design

The study was performed in Melbourne, Australia, between September 1996 and June 1999. The ambulance service has treatment protocols that follow the recommendations of the Australian Resuscitation Council.[19] Patients were enrolled in the study when the following criteria were fulfilled: an initial cardiac rhythm of ventricular fibrillation at the time of arrival of the ambulance, successful return of spontaneous circulation, persistent coma after the return of spontaneous circulation, and transfer to one of four participating emergency departments. The exclusion criteria were an age of less than 18 years for men, an age of less than 50 years for women (because of the possibility of pregnancy), cardiogenic shock (a systolic blood pressure of less than 90 mm Hg despite epinephrine infusion), or possible causes of coma other than cardiac arrest (drug overdose, head trauma, or cerebrovascular accident). Patients were also excluded if an intensive care bed was not available at a participating institution.

After the return of spontaneous circulation had been accomplished outside the hospital, eligible patients were randomly assigned to hypothermia or normothermia according to the day of the month, with patients assigned to hypothermia on odd-numbered days. For these patients, the paramedics began measures in the field to initiate hypothermia by removing the patient's clothing and applying cold packs (CoolCare, Cheltenham, Victoria, Australia) to the patient's head and torso. The treatment of patients assigned to normothermia followed usual prehospital treatment protocols.

On arrival at a participating emergency department, the patients underwent routine initial assessment and treatment, includ-

From the Intensive Care Unit, Dandenong Hospital, Dandenong (S.A.B., M.D.B.); the Intensive Care Unit, Knox Hospital, Wantirna South, Melbourne (S.A.B., M.D.B., B.M.J.); the Metropolitan Ambulance Service, Victoria (S.A.B.); the Department of Emergency Medicine, Monash Medical Centre, Clayton (T.W.G.); the Department of Intensive Care, Austin and Repatriation Medical Centre, Heidelberg (W.S., G.G.); and the Monash University Department of Epidemiology and Preventive Medicine, St. Kilda (K.S.) — all in Australia. Address reprint requests to Dr. Bernard at Dandenong Hospital, David St., Dandenong, VIC 3175, Australia, or at s.bernard@southernhealth.org.au.

ing mechanical ventilation and correction of cardiovascular instability. After an evaluation of neurologic status, all patients were given intravenous midazolam (2 to 5 mg) and vecuronium (8 to 12 mg). Arterial blood gas values, corrected for temperature, were used to adjust the ventilator to maintain a partial pressure of arterial oxygen of 100 mm Hg and a partial pressure of arterial carbon dioxide of 40 mm Hg. The mean arterial blood pressure was maintained between 90 and 100 mm Hg by infusion of epinephrine or nitroglycerin, as indicated. Thrombolytic therapy was administered to patients with electrocardiographic changes suggestive of acute myocardial infarction, unless it was contraindicated. Intravenous heparin was administered if the history, electrocardiogram, or both suggested an ischemic coronary syndrome without infarction. All patients were given a lidocaine bolus (1 mg per kilogram of body weight) followed by an infusion (2 mg per minute for 24 hours) in an attempt to prevent recurrent ventricular tachyarrhythmias. Potassium was given intravenously to maintain a serum level of 4.0 mmol per liter, and insulin was administered subcutaneously to maintain a blood glucose level of 180 mg per deciliter (10 mmol per liter) or less. Aspirin was administered to all patients.

Core body temperature was monitored by reading the tympanic temperature or bladder temperature until a pulmonary-artery catheter was placed. Initial investigations in the emergency department included 12-lead electrocardiography and measurement of arterial blood gases, electrolytes, glucose, creatine kinase (total and MB fractions), and lactate. These measurements were repeated at 1 to 3 hours (on admission to the intensive care unit) and at 6, 12, 18, and 24 hours after arrival at the hospital. Complete blood counts were performed on arrival and repeated at 12 and 24 hours.

After the admission of the patient to the intensive care unit, a pulmonary-artery catheter was inserted, and hemodynamic data were obtained 1 to 3, 6, 12, 18, and 24 hours after arrival at the hospital. Some patients (7 of 39 undergoing hypothermia and 11 of 33 undergoing normothermia) were treated without the use of a pulmonary-artery catheter, as requested by the attending physician in the intensive care unit.

The study was approved by the Medical Standards Committee of the Metropolitan Ambulance Service and the institutional ethics committee at each participating hospital. Because of the emergency conditions under which this study was performed, written informed consent for participation in the study was sought from the next of kin as soon as possible after the arrival of the patient at the hospital.

Treatment Protocol

Patients assigned to hypothermia underwent initial basic cooling measures in the ambulance. After arrival at the hospital, they underwent vigorous cooling in the emergency department (or the intensive care unit if a bed was immediately available), as soon as possible after the initial assessment, by means of extensive application of ice packs around the head, neck, torso, and limbs. When the core temperature reached 33°C, the ice packs were removed, and this temperature was maintained until 12 hours after arrival at the hospital while the patient continued to be sedated and paralyzed with small doses of midazolam and vecuronium, as required, to prevent shivering that might lead to warming. Beginning at 18 hours, the patients were actively rewarmed for the next 6 hours by external warming with a heated-air blanket, with continued sedation and neuromuscular blockade to suppress shivering. Patients assigned to normothermia were also sedated and paralyzed initially, but the target core temperature was 37°C. Passive rewarming was used in these patients if there was mild spontaneous hypothermia on arrival.

After 24 hours, patient care followed the usual intensive care unit protocols. Patients who had regained consciousness underwent extubation and were transferred to a coronary care unit. Active life support was withdrawn from most patients who remained deeply comatose at 72 hours. Patients with an uncertain prognosis underwent tracheostomy and were discharged from the intensive care unit.

Assessment of Outcome

When the patients were ready for discharge from the hospital, they were assessed by a specialist in rehabilitation medicine who was unaware of the treatment group. On the basis of this evaluation, patients were discharged to home, to a rehabilitation facility, or to a long-term nursing facility. Discharge home or to a rehabilitation facility was regarded as a good outcome, whereas death in the hospital or discharge to a long-term nursing facility, whether the patient was conscious or unconscious, was regarded as a poor outcome.

Statistical Analysis

The primary outcome measure was survival to hospital discharge with sufficiently good neurologic function to be sent home or to a rehabilitation facility. Secondary outcome measures included the hemodynamic, biochemical, and hematologic effects of hypothermia. Statistical analysis was performed with the Stata statistical package.[20] Continuous variables, such as vital signs and biochemical results, were analyzed by repeated-measures analysis of variance, which was modeled by generalized estimating equations with unstructured correlation and robust standard errors. Data for some variables were insufficient at certain time points, and for these a first-order autoregression correlation structure with robust standard errors was used. Base-line data (measurements on arrival at the hospital) were compared by t-tests for continuous variables and by the chi-square test or Fisher's exact test for categorical variables. An adjusted odds ratio for a good outcome as compared with a bad outcome was calculated by multivariate logistic regression.

On the basis of our previous study,[16] it was determined that a sample of 62 patients (31 in each group) would be required to show a change in the rate of a good outcome (discharge to home or to a rehabilitation facility) from 14 percent to 50 percent, with a power of 80 percent and a significance level of 0.05. An analysis of results from 62 eligible patients found that the outcome in the control group was better than our previously published rate,[16] but that there was a strong trend toward improved outcome in the hypothermia group. The study was continued for a further 12 months, at which time 84 patients had been eligible for enrollment, 77 had been enrolled, and 72 had been treated according to the correct treatment assignment.

RESULTS

Characteristics of the Patients

Eighty-four patients were eligible for enrollment in the study over a period of 33 months. Data on seven of these patients were excluded from the analysis (five because they were transferred from the initial hospital to a nonparticipating intensive care unit and two because the next of kin refused consent for data collection). Of the remaining 77 patients, 43 were assigned to hypothermia and 34 to normothermia.

The clinical characteristics of the 77 patients are shown in Table 1. Four patients assigned to hypothermia did not receive this treatment because the emergency physician erred by not initiating cooling (three patients) or because the patient was inadvertently rewarmed shortly after admission to the intensive care unit (one patient). One patient who was assigned to normothermia became moderately hypothermic

Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial

Guy L Clifton, Alex Valadka, David Zygun, Christopher S Coffey, Pamala Drever, Sierra Fourwinds, L Scott Janis, Elizabeth Wilde, Pauline Taylor, Kathy Harshman, Adam Conley, Ava Puccio, Harvey S Levin, Stephen R McCauley, Richard D Bucholz, Kenneth R Smith, John H Schmidt, James N Scott, Howard Yonas, David O Okonkwo

Summary

Background The inconsistent effect of hypothermia treatment on severe brain injury in previous trials might be because hypothermia was induced too late after injury. We aimed to assess whether very early induction of hypothermia improves outcome in patients with severe brain injury.

Methods The National Acute Brain Injury Study: Hypothermia II (NABIS: H II) was a randomised, multicentre clinical trial of patients with severe brain injury who were enrolled within 2·5 h of injury at six sites in the USA and Canada. Patients with non-penetrating brain injury who were 16–45 years old and were not responsive to instructions were randomly assigned (1:1) by a random number generator to hypothermia or normothermia. Patients randomly assigned to hypothermia were cooled to 35°C until their trauma assessment was completed. Patients who had none of a second set of exclusion criteria were either cooled to 33°C for 48 h and then gradually rewarmed or treated at normothermia, depending upon their initial treatment assignment. Investigators who assessed the outcome measures were masked to treatment allocation. The primary outcome was the Glasgow outcome scale score at 6 months. Analysis was by modified intention to treat. This trial is registered with ClinicalTrials.gov, NCT00178711.

Findings Enrolment occurred from December, 2005, to June, 2009, when the trial was terminated for futility. Follow-up was from June, 2006, to December, 2009. 232 patients were initially randomised a mean of 1·6 h (SD 0·5) after injury: 119 to hypothermia and 113 to normothermia. 97 patients (52 in the hypothermia group and 45 in the normothermia group) did not meet any of the second set of exclusion criteria. The mean time to 35°C for the 52 patients in the hypothermia group was 2·6 h (SD 1·2) and to 33°C was 4·4 h (1·5). Outcome was poor (severe disability, vegetative state, or death) in 31 of 52 patients in the hypothermia group and 25 of 56 in the normothermia group (relative risk [RR] 1·08, 95% CI 0·76–1·53; p=0·67). 12 patients in the hypothermia group died compared with eight in the normothermia group (RR 1·30, 95% CI 0·58–2·52; p=0·52).

Interpretation This trial did not confirm the utility of hypothermia as a primary neuroprotective strategy in patients with severe traumatic brain injury.

Funding National Institute of Neurological Disorders and Stroke.

Lancet Neurol 2011; 10: 131–39
Published Online December 20, 2010 DOI:10.1016/S1474-4422(10)70300-8
See Comment page 111

Vivian L Smith Center for Neurologic Research, Department of Neurosurgery, The University of Texas Medical School at Houston, Houston, TX, USA (Prof G L Clifton MD, A Valadka MD, P Drever RN, A Conley MD); Seton Brain and Spine Institute, Austin, TX, USA (A Valadka); Department of Critical Care Medicine (D Zygun MD, P Taylor RN) and Department of Radiology (J N Scott MD), University of Calgary, Calgary, AB, Canada; Department of Biostatistics, University of Iowa, Iowa City, IA, USA (Prof C S Coffey PhD); Department of Biostatistics, School of Public Health, University of Alabama, Birmingham, AL, USA (C S Coffey); Silverwind Research, La Veta, CO, USA (S Fourwinds); National Institute of Neurological Disorders and Stroke, Rockville, MD, USA (L S Janis PhD); Baylor College of Medicine, Houston, TX, USA (E Wilde PhD, Prof H S Levin PhD, S R McCauley PhD); Department of Neurosurgery, University of Pittsburgh, Pittsburgh, PA, USA (K Harshman RN, A Puccio RN, Prof D O Okonkwo MD); Division of Neurosurgery, St Louis University, St Louis, MO, USA (Prof R D Bucholz MD, Prof K R Smith MD); Neurological Associates, Charleston, WV, USA (J H Schmidt MD); and Department of Neurosurgery, University of New Mexico, Albuquerque, NM, USA (Prof H Yonas MD)

Introduction

The results of 23 clinical trials of hypothermia treatment involving 1614 patients with severe brain injury have been inconsistent,[1] probably because of differences in trial design. Randomised clinical trials of hypothermia for severe brain injury can be divided into those trials in which hypothermia was used to treat raised intracranial pressure[2–6] and those in which hypothermia was intended as a neuroprotectant, to stop the biochemical cascade after injury. In the former group, hypothermia was started in the first 24 h after injury but continued through the peak period of raised intracranial pressure (3–5 days) or until intracranial hypertension was resolved.[2–6] Four of these five studies reported a decrease in mortality rate or in the percentage of patients having a poor recovery[2–5] accompanied in three by significantly decreased raised intracranial pressure with hypothermia treatment.[2–4] In the latter group of trials, hypothermia was assessed as a neuroprotectant, similar to its use in cardiac arrest, and reached 33–34°C in the first 10 h after injury and continued for a predefined 24–48 h, irrespective of intracranial pressure.[7–9] Studies with this design have all failed to show improved outcome with hypothermia treatment.

We previously reported a multicentre trial[7] of hypothermia for neuroprotection, in which 392 patients with acute brain injury were randomised to normothermia or surface-induced hypothermia. Patients in the hypothermia group reached the target temperature of 33°C a mean of 8·4 h (SD 3·0) after injury. Hypothermia did not improve outcome (relative risk [RR] 1·0, 95% CI 0·8–1·2) and the hypothermia group had a higher rate of hypotension than the normothermia group (p=0·01).[7] However, there was some weak evidence of improved outcomes in patients who were hypothermic on admission and treated with continued hypothermia

Correspondence to:
Prof Guy L Clifton,
6431 Fannin Street, Suite 7.130,
Houston, TX 77030, USA
guy.l.clifton@uth.tmc.edu

compared with those in the normothermia group (p=0·09).[10] We therefore concluded that hypothermia might have been started too late and that hypotension might have affected the results. In the present study, we aimed to assess whether very early induction of hypothermia in patients with severe traumatic brain injury improved outcome at 6 months.

Methods

Patients

For the trial protocol see http://www.uth.tmc.edu/schools/med/neurosurg/Assets/pdf/faculty/NABIS-Hypothermia-IIR-Protocol.pdf

The National Acute Brain Injury Study: Hypothermia II (NABIS: H II) was a multicentre randomised trial of patients with severe brain injury who received either early cooling to 33°C maintained for 48 h or treatment at normothermia. Patients were enrolled either during transport to the hospital or in the emergency department. The enrolment window was increased from 2 h to 2·5 h after injury in December, 2006, to increase enrolment.

Inclusion criteria were age 16–45 years, non-penetrating brain injury, and not responsive to instructions. There were two sets of exclusion criteria. The initial set of inclusion and exclusion criteria were measured in the field or upon arrival at the emergency department but before resuscitation and trauma assessment in the emergency department. At randomisation, patients were excluded if they had suspected pregnancy, systolic blood pressure less than 110 mm Hg, diastolic blood pressure less than 60 mm Hg, sustained heart rate greater than 120 beats per minute, or if they could not be reached by study-affiliated personnel within 2·5 h of injury. The second set of exclusion criteria were measured after complete assessment and resuscitation. At this stage, patients were further assessed for the presence of a severe brain injury (Glasgow coma scale score of 3–8 after resuscitation) without life-threatening associated injuries. Exclusion criteria were Glasgow coma scale score of 3 with nonreactive pupils, Glasgow coma scale score of 7–8 with normal brain CT scan, inability to measure an accurate Glasgow coma scale score, abbreviated injury severity score of 4 or greater for organs other than the brain,[11] systolic blood pressure less than 110 mm Hg, diastolic blood pressure less than 60 mm Hg, persistent hypoxia (oxygen saturation <94%), or a positive pregnancy test.

Consent was waived unless a family member was immediately able to provide consent. The trial protocol and the decision to waive consent were approved by institutional review and ethics boards of each participating centre.

Randomisation and masking

Patients were randomly assigned (1:1), stratified by centre, to hypothermia or normothermia. The randomisation sequence was generated by the study biostatistician with a random number generator. The secretary at the trial-coordinating centre (University of Texas Medical School at Houston, Houston, TX, USA) placed treatment assignments into numbered opaque envelopes, which were sealed and mailed to each trial centre. Patients were enrolled at six centres: University of Texas Health Science Center at Houston, TX, USA; University of Calgary, AB, Canada; University of Pittsburgh, Pittsburgh, PA, USA; St Louis University, St Louis, MO, USA; Charleston Area Medical Center, Charlestown, WV, USA; and University of New Mexico, Albuquerque, NM, USA. Randomisation was done at each trial centre by study nurses after opening sequentially numbered envelopes. For eligible patients who were enrolled during transport to the hospital, the emergency service personnel contacted the study nurse at the local trial centre by telephone, who informed the emergency service personnel of the treatment assignment.

Investigators who assessed the outcome measures were masked to treatment allocation. Emergency service personnel, study nurses involved in randomisation, and personnel who managed the patients were unmasked to treatment allocation.

Procedures

Temperatures below 35°C are associated with increased mortality in patients with multiple trauma.[12] Therefore, patients who were randomised to hypothermia were maintained at 35°C by intravenous instillation of up to 2 L of cold crystalloid and application of wet sheets or gel packs until completion of the trauma assessment. Those assigned to normothermia were maintained at 37°C.

Patients who did not meet any of the second set of exclusion criteria and who were randomly assigned to the hypothermia group were cooled to 33°C by the Arctic Sun Temperature Management System (surface cooling; Medivance, Louisville, CO, USA), use of room temperature ventilated air, continuation of chilled intravenous crystalloid, and gastric lavage with cold water. Patients in the hypothermia group were maintained at 33°C for 48 h and then rewarmed by 0·5°C every 2 h, regardless of levels of intracranial pressure. Patients randomly assigned to normothermia who did not meet any of the second set of exclusion criteria were maintained at 37°C. Patients who were initially randomised but who met the second set of exclusion criteria were not given any further trial treatment.

Morphine was administered to all patients for at least 72 h at a dose of 0·05–0·10 mg/kg/h, a lower dose than in our previous study,[7] to reduce the risk of hypotension. Pancuronium bromide was administered to patients assigned to hypothermia for at least 72 h and to those assigned to normothermia as needed. Intermittent doses of fentanyl (1·0 μg/kg) were administered to all patients for pain management. Phenytoin was administered to all patients at 20 mg/kg followed by maintenance doses for 7 days. Blood gases were not corrected for body temperature. Low serum potassium and magnesium concentrations were treated with intravenous replacement, except preceding and during rewarming. The protocol stated that partial pressure of arterial carbon dioxide less than 30 mm Hg should be avoided where possible.[13]

ORIGINAL CONTRIBUTION

Intravenous Drug Administration During Out-of-Hospital Cardiac Arrest

A Randomized Trial

Theresa M. Olasveengen, MD
Kjetil Sunde, MD, PhD
Cathrine Brunborg, MSc
Jon Thowsen
Petter A. Steen, MD, PhD
Lars Wik, MD, PhD

Context Intravenous access and drug administration are included in advanced cardiac life support (ACLS) guidelines despite a lack of evidence for improved outcomes. Epinephrine was an independent predictor of poor outcome in a large epidemiological study, possibly due to toxicity of the drug or cardiopulmonary resuscitation (CPR) interruptions secondary to establishing an intravenous line and drug administration.

Objective To determine whether removing intravenous drug administration from an ACLS protocol would improve survival to hospital discharge after out-of-hospital cardiac arrest.

Design, Setting, and Patients Prospective, randomized controlled trial of consecutive adult patients with out-of-hospital nontraumatic cardiac arrest treated within the emergency medical service system in Oslo, Norway, between May 1, 2003, and April 28, 2008.

Interventions Advanced cardiac life support with intravenous drug administration or ACLS without access to intravenous drug administration.

Main Outcome Measures The primary outcome was survival to hospital discharge. The secondary outcomes were 1-year survival, survival with favorable neurological outcome, hospital admission with return of spontaneous circulation, and quality of CPR (chest compression rate, pauses, and ventilation rate).

Results Of 1183 patients for whom resuscitation was attempted, 851 were included; 418 patients were in the ACLS with intravenous drug administration group and 433 were in the ACLS with no access to intravenous drug administration group. The rate of survival to hospital discharge was 10.5% for the intravenous drug administration group and 9.2% for the no intravenous drug administration group ($P=.61$), 32% vs 21%, respectively, ($P<.001$) for hospital admission with return of spontaneous circulation, 9.8% vs 8.1% ($P=.45$) for survival with favorable neurological outcome, and 10% vs 8% ($P=.53$) for survival at 1 year. The quality of CPR was comparable and within guideline recommendations for both groups. After adjustment for ventricular fibrillation, response interval, witnessed arrest, or arrest in a public location, there was no significant difference in survival to hospital discharge for the intravenous group vs the no intravenous group (adjusted odds ratio, 1.15; 95% confidence interval, 0.69-1.91).

Conclusion Compared with patients who received ACLS without intravenous drug administration following out-of-hospital cardiac arrest, patients with intravenous access and drug administration had higher rates of short-term survival with no statistically significant improvement in survival to hospital discharge, quality of CPR, or long-term survival.

Trial Registration clinicaltrials.gov Identifier: NCT00121524

JAMA. 2009;302(20):2222-2229 www.jama.com

INTRAVENOUS ACCESS AND DRUG ADministration are integral parts of cardiopulmonary resuscitation (CPR) guidelines.[1] Millions of patients have received epinephrine during advanced cardiac life support (ACLS) with little or no evidence of improved survival to hospital discharge.[1,2] The use of epinephrine is based on preclinical evidence of increased cerebral and coronary perfusion by redirected peripheral blood flow.[1,2] Beneficial short-term effects of epinephrine have been shown in animal studies,[3-5] but there is increasing concern for increased myocardial dysfunction[6,7] and disturbed cerebral microcirculation after cardiac arrest.[8] Epinephrine was an independent predictor of poor outcome in a large retrospective registry study,[9] but this observational, nonrandomized study cannot prove a causal relationship. Despite its near-universal use, epinephrine has, to our knowledge, not been tested in a randomized controlled study with a no-drug comparison group.

If a negative association between epinephrine and survival is causal, it may be due to the drug or to inadequate CPR quality associated with drug adminis-

Author Affiliations: Institute for Experimental Medical Research (Drs Olasveengen and Wik), Centre for Clinical Research (Ms Brunborg), and National Competence Centre for Emergency Medicine (Dr Wik), Departments of Anesthesiology (Dr Olasveengen) and Ambulance (Mr Thowsen and Dr Steen), Surgical Intensive Care Unit (Dr Sunde), and Faculty Division UUH (Dr Steen), Oslo University Hospital, Oslo, Norway. **Corresponding Author:** Theresa M. Olasveengen, MD, Institute for Experimental Medical Research, Oslo University Hospital, Ullevaal, N-0407 Oslo, Norway (t.m.olasveengen@medisin.uio.no).

tration. Drug administration includes time-consuming factors like establishing intravenous access, preparation, and administration of drugs and saline, thereby potentially removing focus from good-quality CPR. There are recent reports of poor-quality CPR and protocol adherence among professional CPR providers,[10,11] and some consider intubation and intravenous access more important than giving good-quality chest compressions.[12] With inadequate CPR quality, effects of drugs administered peripherally also may be diminished or absent.[13] Because there are no randomized controlled studies showing improved survival to hospital discharge with any drugs routinely administered during CPR, we concluded such a study was warranted.

In this prospective, randomized controlled trial of intravenous drug administration during out-of-hospital cardiac arrest, we compared outcomes for patients receiving standard ACLS with intravenous drug administration (control) and patients receiving ACLS without intravenous drug administration (intervention).

METHODS

The city of Oslo has a single-tiered emergency medical service system administered by the Oslo University Hospital for a population of 540 000. On weekdays between 7:30 AM and 10:00 PM, an ambulance staffed by 2 paramedics and an anesthesiologist functions on the same level as the regular paramedic-staffed ambulances. Until January 2006, ACLS was performed according to the International Guidelines 2000,[14] with the modification that patients with ventricular fibrillation received 3 minutes of CPR before the first shock and between unsuccessful series of shocks.[15] The European Resuscitation Council Guidelines for Resuscitation 2005[16] were implemented in January 2006, incorporating this same modification of 3-minute periods of CPR. Defibrillators in manual mode are used and endotracheal intubation is standard for securing the airways. Two ambulances are routinely dispatched for suspected cardiac arrest. The physician-staffed ambulance is dispatched whenever available.

All hospitals in Oslo have goal-directed postresuscitation protocols including therapeutic hypothermia regardless of initial rhythm or arrest etiology.[17] A prehospital 12-lead electrocardiogram is routinely transmitted to the cardiologist on call after return of spontaneous circulation (ROSC). If coronary angiography is indicated for possible percutaneous coronary intervention, patients are transported directly from the scene to 1 of 2 university hospitals (Oslo University Hospital, Ullevaal and Rikshopitalet) with this capacity 24 hours per day.

Study Design and Recruitment

All patients older than 18 years with nontraumatic, out-of-hospital cardiac arrests between May 1, 2003, and April 28, 2008, were randomized by ambulance personnel on-site. Simple randomization occurred directly after ambulance personnel confirmed the cardiac arrest and then opened the sealed envelopes provided by the investigators. Patients were randomized to receive either ACLS with access to intravenous drug administration (intravenous group) or ACLS without access to intravenous drug administration (no intravenous group). In the no intravenous group, intravenous access was to be established 5 minutes after ROSC, and drugs could then be given if indicated.

Exclusion criteria were (1) cardiac arrest witnessed by ambulance crew because these patients almost always have an intravenous needle in place at the time of the cardiac arrest, (2) resuscitation initiated or interrupted by physicians outside of the ambulance team, or (3) cardiac arrest induced by asthma or anaphylactic shock (which were the last criteria added in October 2006). The study was approved by the regional ethics committee. Informed consent for inclusion was waived as decided by this committee, but was required from survivors with 1-year follow-up.

Equipment and Data Collection

Standard defibrillators (LIFEPAK 12 Physio-Control, Medtronic, Redmond, Washington) were used. Electrocardiograms with transthoracic impedance signals from these defibrillators were routinely transferred to a server at the National Competence Center for Emergency Medicine (Oslo, Norway) following cardiac arrest. Utstein cardiac arrest forms[18] routinely completed by paramedics were submitted to the study supervisor along with a copy of the ambulance run sheet. Automated, computer-based dispatch center time records supplemented ambulance run sheets with regard to response intervals. For admitted patients, additional hospital records were obtained.

All trial data were documented according to the Utstein style.[18] The primary end point was survival to hospital discharge. Secondary outcomes were 1-year survival, survival with favorable neurological outcome (using cerebral performance categories from 1 to 4),[18] hospital admission with ROSC, and quality of CPR (ie, chest compression rate, pauses, and ventilation rate). The study was monitored annually with interim analysis by an external researcher who did not reveal any results to the investigators.

Data Processing

Data from each case were viewed and annotated using CODE-STAT 7.0 (Physio-Control, Medtronic) for detection of ventilations and chest compressions by changes in transthoracic impedance. Written information from patient report forms and locally adapted Utstein style forms were compared with typical changes in CPR patterns as shown using CODE-STAT 7.0. Initial rhythm assessment registered on patient report forms were confirmed by these electrocardiographic recordings if possible. Time without spontaneous circulation, time without compressions during time without spontaneous circulation (hands-off time), preshock pauses, compression rate and actual number of compressions, and ventilations per minute were calcu-

Contains Nonbinding Recommendations

参考資料３－８

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

Exception from Informed Consent Requirements for Emergency Research

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

March 2011

21 CFR 50.24 **APPENDIX A**

The text of 21 CFR 50.24 appears below:

Subpart B--Informed Consent of Human Subjects Sec. 50.24, Exception from informed consent requirements for emergency research.

(a) The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.

(2) Obtaining informed consent is not feasible because:

(i) The subjects will not be able to give their informed consent as a result of their medical condition;

(ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and

(iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

(3) Participation in the research holds out the prospect of direct benefit to the subjects because:

(i) Subjects are facing a life-threatening situation that necessitates intervention;

(ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and

(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

(4) The clinical investigation could not practicably be carried out without the waiver.

(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.

(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.

(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least:

(i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;

(iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

(iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and

(v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in

the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

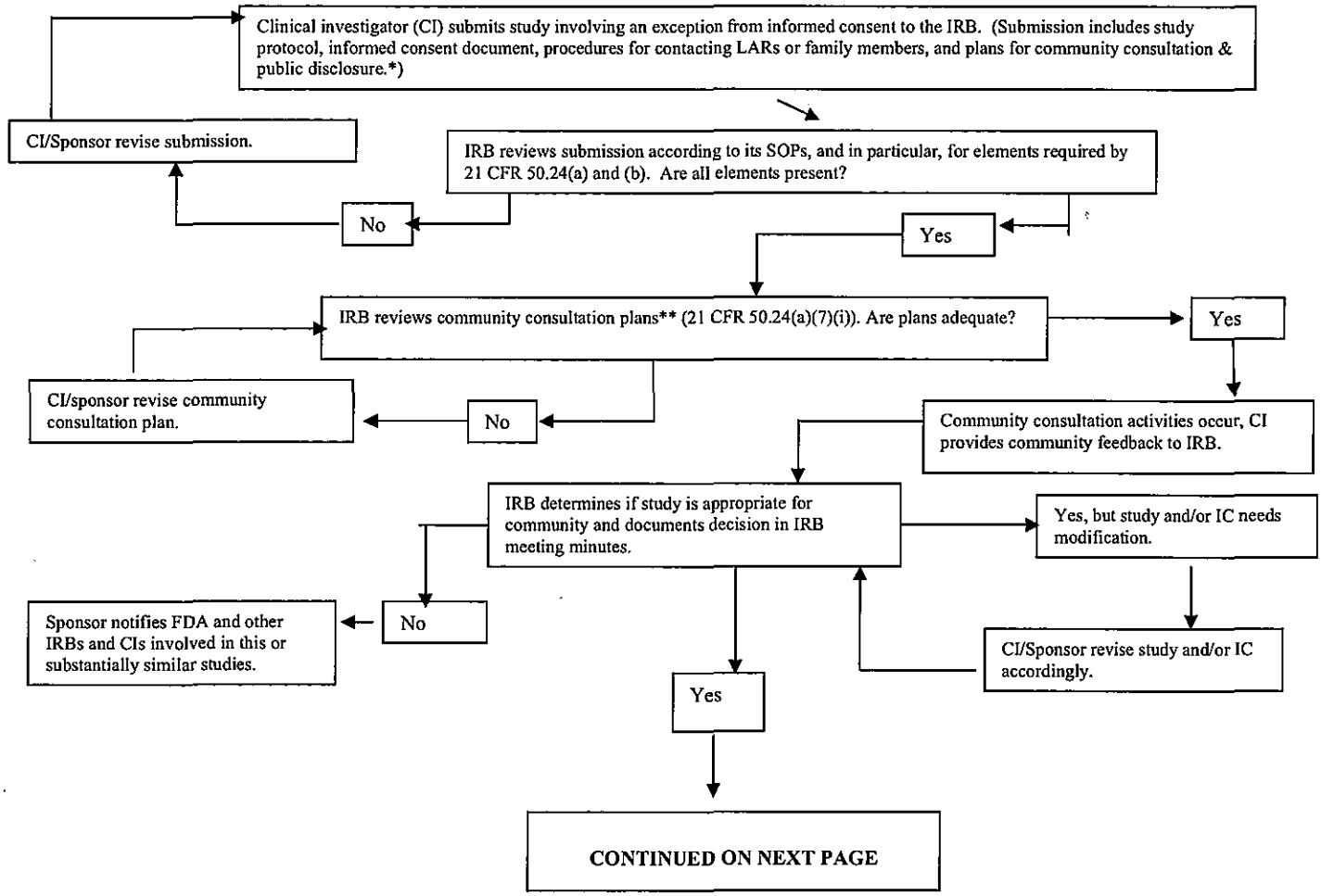
(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

APPENDIX C

SUGGESTED FLOW CHART FOR 50.24 STUDIES

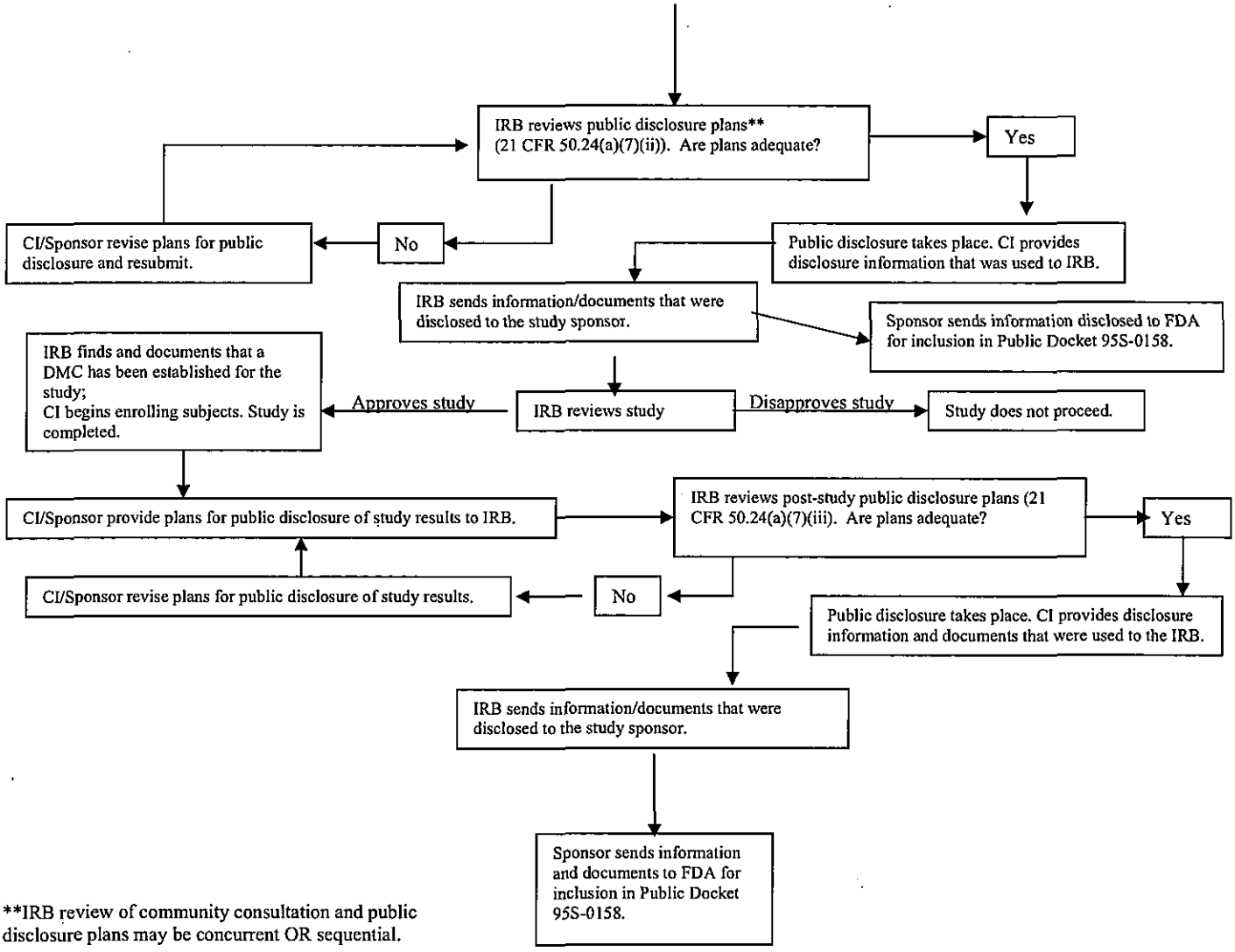
(This is a graphic representation of one way to fulfill requirements for studies conducted under 21 CFR 50.24. Alternative approaches may also be used.)



*The investigation plan for the study, community consultation plans and public disclosure plans may be revised one or more times based on feedback received during the IRB's review and the community consultation/public disclosure process

SUGGESTED FLOW CHART FOR 50.24 STUDIES
(Continued from Previous Page)

(This is a graphic representation of one way to fulfill requirements for studies conducted under 21 CFR 50.24. Alternative approaches may also be used.)



**IRB review of community consultation and public disclosure plans may be concurrent OR sequential.

参考資料３－９

Code of Medical Ethics

of the American Medical Association

Council on Ethical and Judicial Affairs

Current Opinions with Annotations

2006–2007 Edition

Annotations prepared by the
Southern Illinois University Schools of Medicine and Law

AMA
AMERICAN
MEDICAL
ASSOCIATION

7.00 Opinions on Physician Records

8.00 Opinions on Practice Matters

AMA
AMERICAN MEDICAL ASSOCIATION

Opinion 8.085 - Waiver of Informed Consent for Research in Emergency Situations

The current state of emergency medicine and research has resulted in the application of standard treatments that often have not been scientifically evaluated for safety and effectiveness and may render unsatisfactory outcomes. Given the insufficiency of standard treatment alternatives, it is appropriate, in certain situations and with special safeguards, to provide experimental treatments without obtaining the informed consent of the subject. However, in order to protect the rights and welfare of the subjects, several conditions must be met:

(1) This type of research is limited to emergency, life-threatening situations, and may involve only experimental treatments that are ready for trials involving human subjects.

(2) The subject must lack the capacity to give informed consent for participation in the research.

(3) The window of opportunity for intervention must be so narrow as to make obtaining surrogate consent unfeasible.

(4) Obtaining prospective informed consent for the protocol must not be feasible (ie, the life threatening emergency situation could not have been anticipated).

(5) The experimental treatment must have a realistic probability of benefit equal to or greater than standard care.

(6) The risks associated with the research should be reasonable in light of the critical nature of the conditions and the risks associated with standard treatment.

(7) Where informed consent is waived, subjects or their representatives must be informed as soon as possible about inclusion in the study and asked to consent to further participation. Subjects, or their representatives, may choose to discontinue participation at any time after being fully informed about the possible consequences. Additionally, if the patient dies while participating in the research protocol, the patient's family or representative must be informed that the patient was involved in an experimental protocol.

(8) Community input should be sought prior to approval of the protocol, and public disclosure should be made of study results. Fair randomization of research subjects should be given thorough consideration. Moreover, an independent data monitoring board should be established to oversee the ongoing trial. (I, V)

CEJA Report 1 – A-97
Waiver of Informed Consent for Emergency Room Research

INTRODUCTION

Emergency medicine involves the treatment of a highly diverse and critically ill population of patients. A number of physicians consider many standard treatments for emergency conditions to be inadequate. Efforts to assess new treatments in this field are uniquely constrained by the limitations on consent for research participation by seriously incapacitated patients. Treatment of many severe emergency conditions, including myocardial infarction, stroke, head injury and hypothermia, must rely on long-established practices which produce less-than-satisfactory results in many patients. The American College of Emergency Physicians notes that "we have an obligation to ensure that the American public receives the benefit of improvement in acute care medicine. Such improvement can only come about through continued biomedical research into the causes of and treatments for injury and illness."[1]

Research involving human subjects requires obtaining informed consent from patients or their surrogate decision-makers prior to enrollment in any clinical trial. This is designed to safeguard patient autonomy and protect vulnerable populations from assuming undue research risks. Existing federal regulations had allowed an Institutional Review Board (IRB) to approve a waiver of informed consent only when the research involved minimal risk. Investigators, arguing that this limitation unduly hinders scientific advance, petitioned the federal regulatory agencies (*i.e.*, the Food and Drug Administration (FDA) and Department of Health and Human Services (HHS)) to revise their stance. The FDA released proposed rules in the fall of 1995 and final regulations on October 2, 1996.

To date, the American Medical Association has endorsed application only of standard treatment in emergency cases when consent cannot be secured for clinical investigation.[2] In this report, the Council recognizes the need for improved emergency treatments and acknowledges the considerable safeguards that investigators and regulators can put in place to make emergency research involving human subjects, in the absence of informed consent, safe and effective. Initially, it is important to distinguish between research conducted on emergency patients, and the use of emergency treatment. The latter is permitted in most cases – emergency situations constitute an established exception to informed consent requirements. The former, research involving emergency patients, is the concern of this report.

CURRENT STATE OF EMERGENCY MEDICINE

Emergency care, by its very nature, sometimes involves poor odds for recovery from a serious event. The efficacy of standard therapies often has gone unproven because of the great challenge involved in designing a protocol to assess them. Physicians have become increasingly frustrated with treatment modalities resulting in generally poor outcomes. Some have even adopted innovative treatment methods independently of any opportunity to assess them. In one instance, an IRB was forced to reject a randomized clinical trial comparing high-dose epinephrine with standard-dose epinephrine in cardiac arrest, even though some of the clinicians in the institution were already using the high-dose "test product" on a regular basis.[3] Given the public's high expectations for the medical profession in this context, it is essential that a good means is sought for both assessing present standard treatments and developing new improved ones.

In addition to its urgent nature, emergency care differs from other forms of care in many important ways. The array of conditions encompassed by this field is diverse, including

cardiac arrest, severe head injury, stroke, drug overdose and other catastrophic medical events. Several different practice environments exist, from out-of-hospital emergency response settings, to hospital emergency departments, to inpatient hospital units. In addition, patients receiving this care almost never have an established relationship with the physician providing the care. The often instantaneous response required of emergency physicians places them in the unique position of presuming that all possible treatment should be provided. Traditionally, life-saving treatment in the event of an illness or injury which incapacitates the patient is assumed to be in compliance with patient preferences.

PAST PROFESSIONAL AND REGULATORY REQUIREMENTS

Emergency research involves a small but crucial portion of the clinical research currently being conducted. Consistent with its concern for the individual patient and its objection to enrolling patients in research against their will, the Council on Ethical and Judicial Affairs has stated that: "Where emergency treatment is necessary, the patient is incapable of giving consent, and no one is available who has the authority to act on the patient's behalf, consent for standard treatment only is assumed."[4]

Emergency clinicians, researchers and institutional review boards (IRBs) have long called for revision of federal guidelines which failed adequately to recognize the unique situation of emergency research.[5] Previous guidelines from the FDA and HHS were too incongruous with one another to make research possibilities clear to those reviewing proposed protocols.[6] FDA guidelines allowed for the emergency use of a test article (*i.e.*, experimental treatment) – waiving both the consent requirement and prospective IRB review (retrospective approval is required) – when 1) the subject is confronted by a life threatening situation, 2) informed consent cannot be obtained, 3) there is no time to obtain surrogate consent, and 4) there is no approved alternative treatment available that provides an equal or greater likelihood of saving the subject's life.[7] This does not constitute authorization to conduct a research study, but only permits a single use of an intervention (although in theory there may be multiple "single-uses"). Because these regulations were designed for emergency treatment situations, they were not applicable to most research involving emergency patients. In the latter situation, although the standard treatment may have an equal or greater possibility of saving the subject's life, the experimental treatment may have the potential to greatly increase the subject's level of functioning (condition 4). For example, the standard treatment may have a 50% chance of saving the subject's life, but a 90% chance that the subject will be severely disabled. The experimental treatment may have an equal or lower chance of saving the subject's life, but offer only a 60% possibility that the subject will be severely disabled. This balancing of risks (greater chance to live with lower functioning vs. less chance to live, but a high level of functioning associated with survival; or extremely low chance of survival vs. unknown chance of survival) is exactly the kind of thing the subject or surrogate is supposed to consider when making a decision about entering the study. In the absence of informed consent, the question raised by this policy is whether researchers can presume consent under certain circumstances. For instance, can researchers apply a "reasonable person standard" in deciding which risks potential subjects would agree to?

Unlike the FDA rules, the HHS policy did not allow any waiver of prospective IRB approval, but did allow a waiver of informed consent requirements when 1) the research involved no more than minimal risk, 2) the rights and welfare of the subjects would not be adversely affected, 3) the research could not be carried out without the waiver, and 4) the subjects would be informed after participation.[8] This position reflected a balance between the need for advances in scientific knowledge, and protection of individual inviolability. Thus, where minimal risk was involved, the regulations were in effect allowing subjects to be enrolled without informed consent, whether or not a reasonable person would have agreed to participate. Since the risks were small, the need for scientific advance in this context was

thought to outweigh autonomy concerns. In fact, one could argue that most people (or the hypothetical reasonable person) would agree to minimal risk research, and thus that this was just another case of presumed consent. Although the rule seemed straightforward on its face, it was more difficult to apply than first appears. Minimal risk was incurred when "the probability and magnitude of harm or discomfort anticipated in the research [were] not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[9] No additional guidance was given on how to establish which risks are ordinarily encountered in daily life (*e.g.*, the probability and magnitude of the risks associated with driving a motor vehicle are quite high), nor whose life we should consider (*e.g.*, a critically ill patient who may be exposed to a number of high risk treatments on a daily basis, or the average non-ill person). Notwithstanding the lack of explanation regarding "minimal risk", many researchers and clinicians felt that the severe conditions and treatments represented in emergency medicine were incompatible with this concept. Therefore neither the FDA rules nor the HHS guidelines nor some combination of the two, since they actually appeared to be incompatible with each other, allowed for research with emergency subjects.

Moreover, agency clarification of the rules surrounding waiver of informed consent were somewhat inconsistent. The National Institutes of Health (NIH) and FDA both halted studies due to concerns over the consent process.[10] In contrast, in July 1995, the Secretary of HHS approved a waiver of existing rules for the National Acute Brain Injury Study, funded by the NIH. Although the study involved greater than minimal risk, the secretary recognized that the research was of such importance as to exempt the trial from the usual requirements.[11] Also, in 1990, the FDA approved a waiver for military combat circumstances, allowing the use of investigational drugs in circumstances when obtaining informed consent is unfeasible and withholding the treatment would be contrary to the best interests of the military personnel.[12] Additionally, in 1994, the FDA permitted enrollment of incompetent patients in a high risk trial of polyethylene glycol-conjugated superoxide dismutase treatment for severe closed head injury without any explanation for the apparent exception to the waiver rules.[13] The inadequacy of the past rules not only resulted in inconsistent judgments by the regulatory agencies, but also forced the research establishment to develop creative justifications for granting approval to emergency research protocols.

Unsatisfied with the ambiguous existing guidance, researchers and IRBs began to develop their own paradigms within which they could assess proposed research modalities. Adherence to the principle of deferred consent, where a proxy would authorize continued participation in the protocol subsequent to the patient's enrollment, prevailed for several years, permitting some research to go forward. More recently, the term "ratification" has been applied to reflect this reasoning more genuinely. In 1993, however, the NIH Office for the Protection of Research Risks (OPRR) discredited this rationale by questioning its legality. In a letter to IRB chairs, OPRR reiterated its policy of prospective informed consent for research participation and referenced the language of the waiver provision as the only exception. It also declared that deferred consent or ratification did not constitute informed consent under the HHS regulations.[14]

Other methods of meeting the regulatory informed consent requirements have been proposed. One possibility, advance consent, involves securing permission for research participation in the event of future incapacitation. This proposal may seem unwieldy, but might be supported by widespread completion of advance directives documenting preferences on such research. However, this is likely to be hindered by the fact that only a relatively small percentage of the population complete an advance directive, as well as by the need to indicate with a high degree of specificity the type of research in which one would be willing to participate. Moreover, generic advance directive legislation is designed for use in directing future treatment and thus may not apply to the research context. Alternatively, there may

be research particular to a specific condition for which the patient population in a given geographic area could be targeted for advance consent. This, however, is more likely to work with non-emergency research where it is easier to identify the target population. Another option is to require consent for potential critical research upon hospital admission.[15] This may allow some emergency research to occur (*e.g.*, that which is done in pre-specified inpatient units) but would exclude many emergency patients. Obtaining advance consent from the majority of emergency patients, who by definition are unlikely to have anticipated an emergency event, would require some mechanism for widespread authorization. In theory, integrated health plans could solicit preferences for emergency research participation in the course of enrolling patients. However, given the present difficulties in providing full information on health plans to new enrollees, it may be unlikely that the discerning of research preferences will be given a high priority. Even if it were, the informed consent might be compromised by the circumstances. In general, then, advance consent is an impractical means of surmounting the informed consent difficulties in this context. Proxy consent, although a more accepted means of achieving consent, is also problematic. Proxy consent often cannot be secured within the short time before the research treatment is necessary. Such consent is also not always reliable since there is evidence that relatives may be more cautious about consent to unproven treatment than the actual patient would have been upon presentation of treatment alternatives.[16]

NEW REGULATIONS

On October 2, 1996, new regulations were put forth by FDA creating an exception from informed consent requirements when:

(1) subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and a controlled investigation is necessary;
(2) obtaining informed consent is not feasible;
(3) research participation offers the possibility of direct therapeutic benefit to the subjects;
(4) the investigation could not practicably be carried out without the waiver; and
(5) additional protections of the rights and welfare of the subjects are provided.[17]

An IRB must be assured that each of the conditions is met. Moreover, a licensed physician who is not involved in the investigation must concur with the IRB's approval of the waiver of informed consent. Addition protections must include, at minimum, community consultation prior to IRB approval, public disclosure of intent to begin the study and of results following completion of the study, creation of an independent data monitoring committee to oversee ongoing research, and provision of an opportunity for family members to object to the subject's participation.[18] HHS has issued an assurance that researchers who comply with the FDA regulations will not be in violation of HHS regulations. Moreover, future revisions of the HHS regulations will be congruent with the new guidelines.

ETHICAL ARGUMENTS

The ethical debate surrounding waiver of informed consent for research participation is based upon a concern with protecting patient autonomy. The prospect of enrolling critically ill patients into research protocols without explicit consent certainly raises concerns about exploiting certain vulnerable populations in pursuit of scientific data. Indeed, in every group of individuals enrolled in research without explicit consent, it is likely that some would have wanted only standard treatment. However, many standard treatments in the realm of emergency medicine are inadequate and untested. In this situation, there may be new treatments which, though also unproven, offer the prospect of improved therapy. In such instances, where the comparative efficacy of the standard and experimental treatments is

unknown, it may be appropriate to randomize patients to one treatment or another in a clinical trial.[19]

The argument can be made that a reasonable patient presented with less than good outcomes from standard treatment or unknown outcomes from experimental treatment would choose to have the opportunity for the experimental treatment. In fact, it has been argued that depriving these emergency patients of the experimental treatment because of their inability to consent or give timely proxy consent is discriminatory, preventing this vulnerable group from receiving the best available potential treatment. There is also concern that the unproven standard treatments may, in fact, be harmful. The Belmont Report noted that the principle of beneficence supports research that "makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous."[20]

For this argument to be valid, it is essential that any experimental treatment undergoing clinical trials is anticipated to be at least on par with the standard treatment. The existence of clinical equipoise is essential to any research, but more vitally in cases involving waived informed consent for participation.[21] Clinical equipoise has been described as existing "whenever at least a reasonable minority of medical professionals believe the experimental treatment would be as good as, or better than the standard treatment."[22] Establishing that equipoise exists between standard treatment and an experimental treatment can be a challenge. One good example of the tenuous balance of risks and benefits is trials of tissue plasminogen activator (t-PA) for acute ischemic stroke.[23] In perhaps the most comprehensive study conducted thus far, investigators found that patients who received t-PA were at least 30 percent more likely to have minimal or no disability at the end of a three month period than those who received the placebo. However, the value of this impressive benefit was challenged by a high rate of symptomatic intracerebral hemorrhage in cases where t-PA was administered – 6.4 percent of patients compared with 0.6 percent of patients receiving placebo. Earlier studies of t-PA treatment had been stopped prematurely because of an unacceptable rate of hemorrhage. In this instance, substantial benefits over standard treatment were accompanied by increased risk of a high magnitude.

To what risks is it permissible to expose an unknowing subject? As noted previously, the regulations referred to "minimal risk." The new rules refer to "reasonable risk," a concept which depends on what is known about the experimental treatment, the alternative treatments, and the medical condition.[24] Other commentators, including the Coalition Conference of Acute Resuscitation and Critical Care Researchers (hereinafter "Coalition"), call for the use of a category of so-termed "appropriate incremental risk," which is defined as "any potential risk associated with participating in the research protocol relative to the natural consequences of the medical condition, or any potential risk associated with receiving the experimental treatment relative to receiving the standard treatment for the medical condition."[25] This balancing of risks and benefits particular to a clinical situation is the crux of the justification for permitting more than minimal-risk research without consent. In essence, the patient's prognosis must be so unfavorable that the potential harms associated with the investigational agent are not much greater than the possible outcome from either the standard treatment or no treatment (*e.g.*, death or severe disability). Thus if the standard treatment involves high risk, or even if with treatment there is a high risk of death or disability from the medical condition, then a high-risk investigational treatment may be applied.

REQUIREMENTS FOR WAIVER

Patients in emergency situations are among the vulnerable populations requiring special research protections. In order for this population to be eligible for research participation

without consent the Council requires the following: First, the subject must enter into the critical emergent state suddenly and unexpectedly. If the physician could have anticipated the emergent state (because the subject was critically ill) and thus would have had time to obtain advance consent to research but failed to, consent cannot be waived.[26] Physicians should make efforts to discuss appropriate research options with patients while they still have decision-making capacity. Second, the experimental treatment must have a realistic possibility of benefit at least equal to or greater than standard care. Only where equipoise exists should individuals be deprived of potentially beneficial treatment, or subjected to potential risk of harm. Third, the subject must lack the capacity to give consent. Fourth, the window of opportunity in which to apply the experimental treatment must be so narrow as to preclude obtaining proxy consent. Fifth, the risk associated with the research should be reasonable in light of what is known about the critical nature of the medical condition and the possible alternative treatment options. Sixth, the proposed treatment must be at a sufficient stage of investigation that it is appropriate for use in human trials. Seventh, the research in question must not have been able to be carried out without the informed consent waiver.

Finally, despite the informed consent waiver, the subjects, or their legally authorized representatives, must be informed of their inclusion in the protocol and consent obtained for continued participation as soon as possible after the intervention. The subject, or the proxy, should be assured that he or she may withdraw from the study without repercussions for care. In an instance where withdrawal from the protocol might endanger the subject, the investigator should take steps to ensure that the subject or proxy is instructed about the potential harms and possible alternative treatments so that the decision to withdraw is fully informed. In addition, when a subject dies in the course of the traumatic event, whether or not the death is thought to be related to the research, surviving relatives must be informed that the patient had been enrolled in a research protocol. Previous studies have shown that individuals and their families generally are grateful for having been included in emergency research. It is important to make this disclosure, regardless of the outcome of the particular treatment, since trust in the profession could be undermined by later discovery of participation.

INSTITUTIONAL SAFEGUARDS

It is the responsibility of the investigator to ensure that all ethical requirements are met. Although not all research is covered by the federal regulations that require IRB oversight, the Council strongly recommends that all investigators and institutions develop similar committees to review and approve investigational protocols. In addition, where informed consent requirements will be waived, there should be community input prior to the initiation of the trial. Sources for input might include local public officials and community groups, in addition to members of identifiable populations most likely to be eligible for the research.

An independent data monitoring board should be created to assess the ongoing research. This body would track preliminary study data evaluating whether the risks involved are greater than anticipated, or whether the resulting benefits do not justify the risks.[27] Discrepancies from initial estimates of risks or benefits may result in modification of protocol design or termination of the trial.

CONCLUSION

The general public has high expectations regarding the quality of care to be provided in an emergency medical event. The Coalition Conference of Acute Resuscitation and Critical Care Researchers states: "Patients deserve and expect modern, safe, and effective medical care when they are acutely ill or injured. We believe the public desires advances in acute emergency and critical care and understands that research is required to improve medical

care."[28] The current state of emergency medicine and research has resulted in the application of standard treatments that often have not been scientifically evaluated for safety and effectiveness and may render unsatisfactory outcomes. Given the insufficiency of standard treatment alternatives it is appropriate, with certain safeguards, to provide experimental treatments without obtaining the informed consent of the subject. However, in order to protect the rights and welfare of the subjects several conditions must be met.

RECOMMENDATIONS

The Council makes the following recommendations with respect to waivers of informed consent for emergency research:

1) The proposed research may be conducted only in emergency, life-threatening situations, and only when the experimental treatment is ready for trials involving human subjects.

2) The subject must lack the capacity to give informed consent for participation in the research.

3) The window of opportunity for intervention must be so narrow as to make obtaining surrogate consent unfeasible.

4) Obtaining prospective informed consent for the protocol must not be feasible (*i.e.*, the life-threatening emergency situation could not have been anticipated).

5) The experimental treatment must have a realistic possibility of benefit equal to or greater than standard care.

6) The risks associated with the research should be reasonable in light of the critical nature of the condition and the risks associated with standard treatment.

7) Where informed consent is waived, subjects or their representative must be informed as soon as possible about inclusion in the study and asked to consent to further participation. Subjects, or their representatives, may choose to discontinue participation at any time after being fully informed about the possible consequences. Additionally, if a patient dies while participating in the research protocol, the patient's family or representatives must be informed that the patient was being treated with an experimental protocol.

8) Community input should be sought prior to approval of the protocol, and public disclosure should be made of study results. Fair randomization of research subjects should be given thorough consideration. An independent data monitoring board should be established to oversee the ongoing trial.

参考資料３－10

WAIVER OF INFORMED CONSENT IN PREHOSPITAL EMERGENCY HEALTH RESEARCH IN AUSTRALIA

Amee Morgans
Research Fellow, Department of Community Based Emergency Health and Paramedic Practice, Monash University
Correspondence to Amee Morgans: Amee.Morgans@med.monash.edu.au

Informed consent is a vital part of ethical research. In emergency health care research environments such as ambulance services and emergency departments, it is sometimes necessary to conduct trial interventions or observations without patient consent. At times where treatment is time critical, it may be impossible or inappropriate to seek consent from next of kin. Emergency medicine is one of the few areas where the process of informed consent can be waived to allow research to proceed without patient consent. This article will explore the ethics of informed consent in the prehospital emergency research context. This will include an overview of current Australian guidelines for ethical research, and recent changes in law internationally which have affected the conduct of international emergency health research. An overview of the ethical reasoning behind the waiver of informed consent in emergency research is presented, also addressing issues relating to emergency health research such as proxy consent, unconscious patients, and patient decision making capacity. The unusual circumstances encountered in the prehospital ambulance environment will also be discussed, including the dependent and coercive relationship between patients and ambulance professionals, and a lack of alternatives for care and transport for patients who refuse consent. The conflict arising from differences in medical culture and values between patients and health care professionals will also briefly be discussed. It will be argued that, while emergency care research should not require informed consent due to the restrictions of time and dependent nature of the relationship between patient and health professional, emergency health researchers still have a responsibility to consider the patients' perspective when considering the ethical issues of an emergency research project, particularly in the prehospital environment.

A health emergency is a situation where a patient requires health care in a timeframe restricted by impending ill health or death. This often begins in the 'prehospital' environment such as in the patient's home, or in a public place. Health emergencies in the prehospital environment sometimes involve Ambulance Paramedics, who provide front line emergency health care with limited resources.

The area of emergency health research is a very important one because, when a health condition becomes time critical, early intervention and improved medical care has a higher potential to improve patient health outcomes, including reducing morbidity (Herlitz 2002). It is important, however, to remember that emergency patients are highly dependent on medical care and, as such, are a vulnerable population with diminished autonomy deserving extra protection (Biros et al. 1995). Emergency patients may face several additional areas of vulnerability in terms of language, age, gender, culture or disability (Moreno et al. 1998). It is important to note that this article pertains to informed consent for inclusion in *research*, not consent for *medical treatment*. Informed consent for medical treatment in the Australian context is addressed in a recent publication by an Australian paramedic (Steer 2007).

Prehospital research comes in many forms and in many settings. Areas of research relating to ambulance paramedics involve trialling health care interventions and drugs, clinical trials, social and behavioural research and the epidemiological examination of health records. According to the international Cochrane Collaboration which registers and indexes research protocols and meta-analyses, the volume of emergency health research being conducted has increased exponentially over the past twenty years, resulting in the establishment of the Cochrane Prehospital and Emergency Health Field to specifically address this field of research (Cochrane Collaboration 2010). A common research consideration in any type of emergency health study is the issue of informed consent. Even simple studies using de-identified medical records or observation of patient behaviours with no researcher interaction can still threaten the privacy of the patient in some cases (Office of the Health Services Commissioner 2002), and call into question the duty of care of providers of health care to inform the patient of any situational factors which threaten the patient's autonomy and rights to privacy.

This article will explore the issues of informed consent for research in emergency health situations. The process of informed consent will be explored, including the role of patient, carer and community consent, and decision making capacities of those parties involved. This article aims to examine the issues surrounding informed consent in the emergency health field from a patient, researcher and healthcare provider perspective to offer some insight into the conduct of emergency health research in Australia.

GUIDELINES FOR ETHICAL RESEARCH INVOLVING HUMANS IN AUSTRALIA

The guidelines for research ethics in Australia are well documented and used by human research ethics committees when considering research project proposals for ethics approval. Section Four of the *National Statement on Ethical Conduct in Research Involving Humans* (Commonwealth of Australia 2007) considers research involving persons highly dependent on medical care and includes the areas on emergency, neonatal, intensive care, terminal care and unconscious patients, all of which may be applicable to the emergency healthcare context. The guidelines for ethical research are very clear on the research project requirements the committee needs to consider. These are briefly prefaced below.

The opening section of Chapter One clearly states for a Human Research Ethics Committee (HREC) to approve any proposed research project in including any of these emergency health participants, the project must fulfil a set of four major requirements:

1. RESEARCH MERIT: The project must be of significant potential merit. This is the first key factor affecting research project approval. The burden of participation must be outweighed by the potential benefit of the study.
2. JUSTICE: although it may seem unfair to conduct research on people who are in emergency care situations, where the research merit principle is fulfilled, there must be fair access to participation opportunities.
3. RESPECT: where communication is impaired it may be possible to offer information and seek consent in a non verbal or non-written way.
4. BENEFICENCE: The benefit of the research must justify any risks of harm or discomfort to participants. Furthermore, in the section 4.4.6; which addresses the beneficence principles specifically for emergency care research, the guidelines state that the nature of emergency health research means that informed consent may not be possible, therefore a waiver of consent can be granted by committees where the research merit principle is fulfilled and there is a reasonable expectation of benefit of the study.

If these research conditions are considered by a HREC and it is decided that the project has merit and has been designed to align with these ethical principles, The *National Statement* also includes a guide for ethics committees considering a waiver of informed consent for research proposals on this population, and then a process for those projects given a waiver of informed consent to follow:

Section 2.3.4: Waiver of Consent

2.3.5 Only an HREC may grant waiver of consent for research using personal information in medical research, or personal health information. Other review bodies may grant waiver of consent for other research.

2.3.6: Before deciding to waive the requirement for consent (other than in the case of research aiming to expose illegal activity), an HREC or other review body must be satisfied that:

a) involvement in the research carries no more than low risk to participants;

b) the benefits from the research justify any risks of harm associated with not seeking consent;

c) it is impracticable to obtain consent (for example, due to the quantity, age or accessibility of records);

d) there is no known or likely reason for thinking that participants would not have consented if they had been asked;

e) there is sufficient protection of their privacy;

f) there is an adequate plan to protect the confidentiality of data;

g) in case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them (for example, via a disease-specific website or regional news media);

h) the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled;

i) the waiver is not prohibited by State, federal, or international law. (Commonwealth of Australia 2007, 24).

These ethical guidelines show clear opportunity for emergency health research to be approved by ethics committees, even in situations where consent to participate cannot or will not be given. This is referred to as a waiver of informed consent, which can only

be granted in specific situations, including medical emergency (Irvine et al. 2002) and in the interests of public health, for example quarantine situations, where individual autonomy is superseded by community need (Foex 2001).

Once a waiver is granted by an ethics committee, the research must follow a process to minimise the potential harm of not seeking consent. Where a research project seeks consent from the patient or patient's proxy (including his/her next of kin or legal representative), the researcher must take steps to minimise the risk of stress or emotional impact affecting the participant's ability to understand the information or provide consent. The researchers must also ensure that the relationship between people dependent on care and their carers does not impact the decision to participate. Where the researcher is also the treating health professional consent for research should be sought by another independent person.

Where consent is not being sought from the participant or his/her legal representative, then a waiver of informed consent should only be granted where: it is reasonable to believe the patient would normally have consented, all risks to the participant are minimised, and the project is not culturally or morally controversial. Where the project is a health intervention, the research may only be offered a waiver of informed consent where the research has a reasonable possibility of benefit compared to standard care and the risk of participation is justified by the potential benefit, and inclusion is not contrary to the interests of the patient. If all these conditions are fulfilled then an ethics committee can grant HREC approval with a waiver of informed consent, provided that the participant or their legal representatives are informed of their inclusion after their participation, and offered the opportunity to consent to their inclusion, and offer the option of withdrawal without any reduction in care.

THE ETHICAL CONSIDERATIONS OF THE WAIVER OF INFORMED CONSENT FOR EMERGENCY HEALTH RESEARCH

The ethics of the decision to waive informed consent is based upon the balance of beneficence (seeking the best health outcome for patients), whilst still respecting patient autonomy (represented in their right to make their own decisions about treatment and participation in research). However, there is some merit to the argument that if a patient cannot consent to participation, then the research should be conducted with another participant group or in another setting which allows consent (Moscati 2002). There is also the possibility of a HREC approving a two stage consent procedure, where researchers can seek preliminary consent to participate despite the patient's inability to offer full in-

formed consent, and then seek a confirmation of informed consent at a later stage when the patient or legal representative has had time to make an informed choice.

The Australian ethical guidelines for research involving humans in emergency health outlined above ensure that the ethical principle of beneficence is maintained, by allowing research which is reasonably likely to be of equal or greater benefit than the standard treatment (for example, where the intervention's benefits may be demonstrated in animal studies but not yet demonstrated in humans) to proceed, without delaying implementing the intervention to attempt to get patient consent. Conducting emergency health research whilst still respecting patient autonomy in the form of informed consent is constrained by two factors; the potential impairment of the patient's decision making capacity and the need to deliver the research intervention in the shortest time possible. Additionally, the desire to waive consent in emergency health also acknowledges that asking for patient consent in medical emergencies could be seen to be an unfair burden on an already vulnerable patient (Kowey and Ornato 2000). The decision making capacity of any patient experiencing a health emergency can be affected by many factors, including medication, stress, emotion, and the illness or injury that has caused the emergency. A recent article which examined the ethics of informed consent for medical treatment by ambulance paramedics presented six major barriers to informed consent for medical treatment in the prehospital environment (Steer 2007) which are also faced when seeking informed consent for research participation. In brief, these are summarised as extreme time pressure, extreme emotion, information deprivation, resource limitations, conflict at the scene (for example between paramedics and patients, but also between family members and patients) and impaired judgement. These unique circumstances mean that informed consent in the prehospital emergency ambulance environment needs to be specifically addressed as a different set of circumstances to the in-hospital emergency environment, which generally has greater ability and resources to assess and manage patients, additional support to include carers in the decision making process and is and less dependent on one medical practitioner.

The unique prehospital emergency health research situation has resulted in a recent extensive modification of the waiver of informed consent laws in emergency health research in the US (United States Government Printing Office 2000) to restrict emergency research without patient consent. This presumes that emergency patients as a population can give informed consent, and if they cannot, then they are ineligible to be included in research studies. This is based on the logical presumption that not all ambulance cases have patients with impaired consciousness, and some may therefore be eligible to offer informed consent. To consider whether patients can give informed consent, the process

of informed consent must be explored in the context of a health emergency. To be considered true informed consent, five key elements must be present (Foex 2001).

The first key element of informed consent is a disclosure of the information about the proposed trial, including possible positive and negative outcomes. This is difficult to do in a timely manner, and delays the implementation of the research intervention while it is explained. This is a concern in emergency health research, as the 'window of opportunity' for some interventions is restricted by the progress of the patient's condition. Due to the extreme pressure of time encountered in many prehospital cases, (Steer 2007), using explanatory statements in emergency health research is not always feasible. Furthermore, exactly how much information the patient needs to be given to understand the risks and benefits of the proposed research has been debated (Braunack-Mayer 2002). Patient education has been explored in chronic and preventative health situations, and even when patients were informed about their life threatening health situations in a non emergency environment, their understanding and tendency towards compliance can still be problematic (Campbell et al. 1995). Therefore simply giving potential participants an information sheet about a proposed trial may not supply them with sufficient knowledge about the proposed research project. Knowledge levels and patient preferences about informed consent to participate in research were investigated in a small Swedish study of 31 heart attack patients. The study found that despite extensive informed consent processes during the trial's enrolment, two weeks after the trial began the participants had retained little understanding of the trial and their participation. When asked about their preferred informed consent procedure, patients wanted a concise verbal explanation with family present, rather than written information and signed consent, and were concerned about having to sign papers whilst acutely ill or medicated. Patients and carers also preferred medical professionals to make clinical decisions for them, and found the consent procedure was a further burden in a time of great anxiety. This research suggests that even when consent is informed, the understanding and retention of information by both patients and legal representatives, particularly while patients are acutely unwell or medicated, was compromised. Despite these barriers to the full disclosure of information, improvement of information delivery to a simple, understandable format would enrich the provision of information to patients and may allow consent for inclusion in a research trial to be sought where research concepts are relatively uncomplicated. Alternatively, it may also be possible for patients to consent to a deferral of their decision to a medical professional. In some respects, this would seem a paternalistic approach to health care decision making, however, the patient has the right to choose to defer their medical de-

cisions to a medical professional, or at least seek guidance to support their decision making.

The second key element of informed consent is **comprehension** of the information. Comprehension is usually confirmed by asking the patient to explain the information back to the researcher. Accurate comprehension depends on the researcher's ability to present the information in an unbiased manner. The language used to explain research concepts can be coercive, even when efforts are made to present all options even-handedly. For example, there has been some discussion in the literature about whether patients understand the concept of probability, which they confuse with possibility. For example, patients may prefer to believe that if the risk of death is 50%, they will be in the surviving 50%, technically known as 'optimistic bias' (Ji et al. 2004).

There is, therefore, some doubt whether patients can compare the risks and benefits of a trial intervention. In addition to understanding the risks and benefits, emergency health research usually involves complex medical and research language and understanding – such as a 'placebo controlled trial'. Even the potential for patients to confuse treatment with research, and the degree to which they overlap in a health emergency environment (Adams et al. 1992) can confuse patients. Asking patients to understand these complex medical research concepts during a health emergency is not only unfair, but will take time and may cause the patient additional distress. Therefore this research indicates that patients have the potential to confuse treatment and research and misinterpret, and therefore misunderstand, information related to emergency health research. Comprehension of information again comes down to simple information, clear explanation and opportunity to develop an understanding of the research, the potential risks and benefits and the patient's role as a voluntary participant. Adequate comprehension of all these concepts in the prehospital environment may be obtainable in the alert competent patient, however, there is limited time for consideration of all the factors and limited time also impacts on the opportunity for the patient to reflect on whether or not they truly wish to be involved.

Whether patients want to be involved in decision making in health emergencies was partially investigated in a survey of resuscitation consent with hospitalised patients. Of the 152 patients surveyed, 80% believed that the patients should have a say in end of life decisions, and 20% felt that it was the responsibility of the medical staff. Within the same study, 511 health care professionals were surveyed and 99% reported they believed patient should have a say in end of life decisions (Kerridge et al. 1998). These results are supported by other research (Chan 2004). These differences between medical professionals and patients show that the opinions of medical professionals do not always concur with

that of the patients. A qualitative survey compared physicians and patients views of medical risks, and found patients were willing to accept a low risk outcome of death, whereas physicians were not (Davis et al. 1996).

Whether deferral of decision making to health care providers is appropriate has been further investigated via an examination of conflicts between paramedics and patients. Within the prehospital health emergency environment, conflicts between patients and paramedics arose in 14.4% of 607 observed cases (Adams et al. 1992). A conflict was said to have occurred when the paramedics' perceived obligations were in conflict with the patients' wishes. Major areas of conflict were refusal of treatment or transport (27%) threatening circumstances (19%), limitation of resuscitation (14%), patient competence (17%), resource allocation (10%), confidentiality (8%) and truth telling (3%). The study concluded that the paramedics used a paternalistic approach to patient care but tended to err on the side of beneficence. A hypothetical example of this would be if paramedics wanted to convince the patient of the benefits of a particular outcome, such when they preferred to transport a patient with cardiac chest pain to a hospital with a cardiac care facility, when the patients wished to go to a smaller local hospital they are more familiar with. Conflicts between paramedic and patient are further complicated by the potential for liability, for example, for a patient taken to the smaller regional hospital at his or her own request, which could not provide adequate cardiac care, so that the patient died, in which case the paramedics could be considered negligent in their duty of care to the patient (Adams et al. 1992). These reported conflicts between medical staff and patients reflect the underlying priorities of paternalistic style of care, beneficence and autonomy, and further support the waiver of informed consent in emergency research in terms of seeking better health outcomes for patients. However it is also clear that patients wish to have a say in their emergency health care, and that the medical perspective of beneficence, manifested in prolonging life at all costs, is not always what the patient desires.

The third element of informed consent is **voluntariness**. The voluntariness of informed consent in a health emergency is subject to several limitations, one of which is the potential for coercion. A health emergency is very frightening, and a conscious patient will contemplate the implications of the situation. People in general will hope for a positive outcome of a health emergency, making them vulnerable to coercion in the form of false hope (Simpson 2004). Because there is a more desirable outcome, people will generally believe that preferred outcome will occur for them, as shown in a study of patients suffering from life threatening cardiac illnesses (Cooper et al. 1999). In medical health emergencies, patients are highly dependent on medical care from paramedics, and therefore patients may feel that receiving health care depends on them complying with

the paramedics' requests. The potential for a dependent or coercive relationship is made even greater by the stress and emotional response to a health emergency and with reduced time to consider all options presented, therefore impinging on the voluntariness of consent. Unlike the in-hospital environment, there are no alternatives to ambulance paramedics seeking consent. The in-hospital environment allows for a research nurse or hospital staff member unrelated to treatment to approach patients or carers to seek consent to minimise this bias. The lack of alternative sources for emergency health care and transport to hospital make voluntariness problematic in the prehospital emergency health research setting.

The fourth element of informed consent requires that patients are deemed competent to make the decision. Patient decision making capacity is not routinely assessed in ambulance and paramedic practice, only level of consciousness. The Australian ethical guidelines above state that unconscious patients should be excluded from emergency research except for 'minimally invasive observational research, or in research designed *both* to be therapeutic for them and to improve treatment for the condition from which they suffer' (section 4.4.8, page 62). This policy guideline may exclude from research patients who are most at risk from death and impairment and who may therefore most likely to benefit from research (particularly in palliative care, where research trials are sometimes not able to promise a therapeutic benefit for the patient). It can therefore be argued that this stance sacrifices beneficence in the interests of respecting autonomy. There are many such illnesses that involve a loss of consciousness (such as diabetes, trauma, cardiac arrest, resuscitation, asthma, palliative care), all of which are important research areas, and moreover, these are the patients and populations most likely to benefit from optimisation of medical care (Olson 1994).

Excluding patients who are unconscious from emergency health research is also fraught with assumptions about consciousness and consent. The first issue is the definition of unconsciousness. In the Victorian Ambulance Clinical Practice Guidelines (Metropolitan Ambulance Service and Rural Ambulance Victoria 2001, 2009), and the Australasian Triage Scale (Australasian College of Emergency Medicine 2000), used in all Australian hospital emergency departments, the Glasgow Coma Score is used to determine the level of unconsciousness. The scale ranges from 1–15, with fifteen being completely alert and awake, and a score of seven being classified as unconscious. This scale alone indicates that there are varying levels of consciousness, so how conscious do patients need to be before they are capable of providing informed consent? Consciousness alone does not necessarily mean that patients are competent to make decisions about treatment or participation in research trials. It could be argued that paramedics could make an assessment

of decision making capacity, however, to date validated measures of decision making capacity generally only assess memory recall, and have been misused in research for the purposes of legal liability rather than assessing understanding (Welie 2001). The assessment of decision making competence has already been identified as a key opportunity for improvement in the ambulance paramedic skill set (Steer 2007). If decision making competence cannot be assessed in emergency health patients, then there is no assurance that participants were indeed competent to consent to their inclusion in research, and therefore their consent is invalid.

Finally, if participants have achieved all the previous steps in the process of informed consent, they must then decide whether to participate in the research trial, and have their consent recorded appropriately. To give valid consent, the researcher must be sure that patients understood that they had a choice whether or not to participate, and that declining to participate means that they will get standard treatment. In most cases, consent is indicated by signing a form, however, in some situations, this is not feasible. It is possible to seek unwritten consent; however, one complicating factor of unwritten consent is cultural differences in body language. For example, in many Asian countries, nodding implies that the person has heard and understood what has been said, and is used to prompt the conversation partner to keep talking, whereas in Australia, nodding indicates agreement, and can be interpreted as consent (Mkhize 2004). Therefore consent processes must be free of cultural or language biases, which can be assured with good research design and supporting documentation.

As previously argued, none of the five elements of informed consent are able to be adequately guaranteed in the prehospital health emergency environment. Successfully navigating the whole process of informed consent takes time, and therefore it could be argued even attempting this process is not appropriate for research in the prehospital health emergency situation *at all* due to the potential for delayed patient care and the impact of additional stress on an already vulnerable patient. If information provision and comprehension could be assured, and appropriate vehicles for recording consent could be developed, then three of the five elements of informed consent could be attained. However, the fact remains that the prehospital environment is uniquely impacted by the extreme pressure of time (in some cases where minutes make a difference to patient's health outcomes (Steer 2007), inability of paramedics to assess decision making competence, and a heavily dependent and coercive relationship between the paramedic and the patient.

So do we simply refuse to seek consent from patients for prehospital based emergency research? On one hand, it seems futile, as clearly, true informed consent cannot possibly

be obtained in most cases. How then can the patient's perspectives be considered without gaining informed consent in emergency health situations?

Alternatives to patient informed consent have been offered in different types of in-hospital research, such as retrospective or deferred consent. Even these options still involve conducting research on patients without their consent, and therefore still does not respect the patients' autonomy any better than the waiver of informed consent (Foex 2001). Some may argue that proxy consent may be suitable for gaining informed consent of family members for patients to participate in research trials. The Australian ambulance Clinical Practice Guidelines do not allow acceptance of proxy consent unless the patient is a minor or the proxy has an enduring power of attorney (Adams 1993). There is some dispute about whether proxies can make decisions for patients in health emergencies, when research has shown the majority of family members could not consent to resuscitation research due to their highly emotional state and the time required to impart understanding of the research trial and its implications within an appropriate clinical timeframe (Hsieh et al. 2001). Despite this, research also shows that when surveyed about consent for resuscitation, patients believe family members are an important resource in decision making (Kerridge et al. 1998). From the perspective of patient autonomy, gaining consent from a proxy does not improve patient autonomy, as the patients are still not in control of their own health, unless the proxy has been given a power of attorney by the patient. Furthermore, the concept of proxy consent is based on crucial assumptions; firstly, that the proxy will make better decisions on the patient's behalf than will medical professionals, and secondly, that the proxy has the patient's best interests at heart. In some cases, neither of these assumptions will be correct.

The international perspective on informed consent may offer some solutions to this ethical dilemma. Unfortunately, international guidelines on informed consent in health emergency research are inconsistent; both internationally and within individual states, health care systems, research ethics committees and hospitals (Edwards et al. 2004). In the US, approval for research is usually given in the form of case by case approvals, based on research protocols submitted to a Human Research Ethics Committee for approval prior to research commencement. Although the US used to subscribe to a waiver of informed consent system for all emergency health research, similar to the Australian system, the US federal government has extensively modified the guidelines about what types of projects are eligible for the waiver of informed consent (United States Government Printing Office 2000). There has been some suggestion of using a deferred/retrospective consent system (Kowey and Ornato 2000), however, this systems has the same legal li-

ability issues as the waiver of informed consent, and on that basis is unlikely to be approved.

The UK and Europe are experiencing the same issues with informed consent and legal liability, however, they have moved towards a community consent approach. This entails appointing a panel of survivors/carers/patients that approve the research in principle, and therefore offer community based consent. The US based regulations also require that community input should be sought prior to approval of the research proposal (American Medical Association 2003), and that results be made publicly available at the conclusion of the trial. No clauses in the Australian ethical guidelines require community consultation or transparency of results. A community based consultation and consent process would add a tier to the informed consent process to provide some element of patient involvement in the process of emergency health research, which is currently almost completely absent in the waiver of informed consent process.

Community based consent would have to be gained from a representative sample of people with extensive personal experience in dealing with the illness or situation being researched. At present, human research ethics committees do require lay members, however, these people are not necessarily experienced in the matter being considered, and may possess little more knowledge about the illness than is presented to them by the researchers. Therefore it is important for the community directly involved in the illness or situation to be consulted, which could be in the form of the support associations, survivor support groups, or patients and their families or carers themselves. Use of community based consultation would give the patients a voice in the emergency research process, currently absent in Australia.

In conclusion, it has been determined through careful examination of the informed consent process that informed consent does not seem a feasible research process in prehospital health emergencies due mostly to the issues of limited time and patients' questionable decision making capacity, even when conscious, due to the extreme anxiety and distress common to emergency health situations. This waiver of consent is supported in Australia by the National Statement on Ethical Conduct in Research Involving Humans (Commonwealth of Australia 2007), with the exception of unconscious persons in some cases. Within paramedic practice, paternalistic styles of care focusing on beneficence are most often used approaches to patient care, which conflicts with the principle of autonomy for patients.

One possible solution which has been identified internationally is the use of community consent procedures to allow some patient consultation and promote the importance of the patient's perspective when considering a research trial. It is the responsibility of a

Human Research Ethics Committee to assess a research proposal to determine it is of a high standard and is consistent with ethical research guidelines, however it is ultimately the researcher's responsibility to ensure research is conducted ethically; to maximize the benefits, whilst minimizing the risks and respecting the patient and carer perspectives.

These ethical research issues are common to all forms of medical research. The prehospital and emergency care setting is a research situation where patients are particularly vulnerable to violation of their rights. These issues are relevant to all research which requires informed consent, in addition to research where the participant and proxy understanding of the possible outcomes and potential harm is questionable. Most of all, these issues affect anyone who may one day find themselves in the emergency health situation, or having to make decisions about health on behalf of others.

REFERENCES

Adams, J. 1993. 'Ethical challenges in emergency medical services. A special contribution of the Ethics Committee, National Association of Emergency Medical Services Physicians'. *Prehospital and Disaster Medicine* 8 (2): 179–182.

Adams, J G; Arnold, R; Siminoff, L; Wolfson, A B. 1992. 'Ethical conflicts in the prehospital setting'. *Annals of Emergency Medicine* 21 (10): 1259–1265.

American Medical Association. 2003. *E-8.085 Waiver of Informed Consent for Research in Emergency Situations*. Washington: American Medical Association.

Australasian College of Emergency Medicine. 2000. Policy Document: The Australasian Triage Scale. 2000. Accessed 14 February 2003. Available from: http://www.acem.org.au/open/documents/triage.htm

Biros, M; Lewis, R; Olson, C; Runge, J; Cummins, R O; Fost, N. 1995. 'Informed consent in emergency research: Consensus statement from the coalition conference of acute resuscitation and critical care researchers'. *Journal of the American Medical Association* 273 (16): 1283–1287.

Braunack-Mayer, A. 2002. 'The ethics of participating in research'. *Medical Journal of Australia* 177: 471–472.

Campbell, D A; Yellowlees, P M; McLennan, G; Coates, J R; Frith, P A; Gluyas, P A. et al. 1995. 'Psychiatric and medical features of near fatal asthma'. *Thorax* 50 (3): 254–259.

Chan, H. 2004. 'Sharing death and dying; advance directives, autonomy and the family'. *Bioethics* 18 (2): 87–103.

Cochrane Collaboration. 2010. 'Prehospital and emergency health field'. *Cochrane Collaboration* (4 March 2010). Available from: www.cochranepehf.org.

Commonwealth of Australia. 2007. *National Statement on Ethical Conduct in Research Involving Humans*. Canberra: Commonwealth of Australia.

Cooper, A; Lloyd, G; Weinman, J; Jackson, G. 1999. 'Why patients do not attend cardiac rehabilitation: Role of intentions and illness beliefs'. *Heart* 82 (2): 234–236.

Davis, M A; Keerbs, A; Hoffman, J; Baraff, L. 1996. 'Admission decisions in emergency department chest pain patients at low risk for myocardial infarction: Patient versus physician preferences'. *Annals of Emergency Medicine* 28 (6): 606–611.

Edwards, S; Ashcroft, R; Kirchin, S. 2004. 'Research ethics committees: Differences and moral judgement'. *Bioethics* 18 (5): 409–427.

Foex, B. 2001. 'The problem of informed consent in emergency medicine research'. *Emergency Medicine Journal* 18 (3): 198–204.

Herlitz, J. 2002. 'Consent for research in emergency situations'. *Resuscitation* 53 (3): 239.

Hsieh, M; Dailey, M W; Callaway, C. 2001. 'Surrogate consent by family members for out-of-hospital cardiac arrest research'. *Academic Emergency Medicine* 8 (8): 851–853.

Irvine, R; McPhee, J; Kerridge, I. 2002. 'The challenge of cultural and ethical pluralism in medical practice'. *Medical Journal of Australia* 176 (4): 174–175.

Ji, L.-J; Zhang, Z; Usborne, E; Guan, Y. 2004. 'Optimism across cultures: In response to the severe acute respiratory syndrome outbreak'. *Asian Journal of Social Psychology* 7 (1): 25–34.

Kerridge, I; Pearson, S; Rolfe, I E; Lowe, M. 1998. 'Decision making in CPR: Attitudes of hospital patients and healthcare professionals'. *Medical Journal of Australia* 169: 128–131.

Kowey, P; Ornato, J. 2000. 'Resuscitation research and emergency waiver of informed consent'. *Resuscitation* 47 (3): 307–310.

Metropolitan Ambulance Service and Rural Ambulance Victoria. 2001. *Time Critical Guidelines* (Clinical Practice Guidelines). Melbourne: Metropolitan Ambulance Service and Rural Ambulance Victoria.

Metropolitan Ambulance Service and Rural Ambulance Victoria. 2009. *Time Critical Guidelines* (Clinical Practice Guidelines). Melbourne: Metropolitan Ambulance Service and Rural Ambulance Victoria.

Mkhize, N. 2004. *Indigenous Selves and Ethical Decision Making: Towards Dialogue Between Universalism and Communalism in Ethics*. Paper presented at the 7th World Congress of Bioethics, Sydney, Australia. 9th – 12th November 2004.

Moreno, J; Caplan, A L; Wolpe, P R. 1998. 'Updating protections for human subjects involved in research. Project on Informed Consent, Human Research Ethics Group'. *Journal of the American Medical Association* 280 (22): 1951–1958.

Moscati, R. 2002. 'Protection of human subjects in prehospital research'. *Prehospital Emergency Care* 6 (2 Suppl): S18–S23.

Office of the Health Services Commissioner. 2002. *Health Records Act 2001 (Vic): Statutory Guidelines on Research*. Melbourne: Office of the Health Services Commissioner.

Olson, C. 1994. 'The letter or the spirit: Consent for research in CPR'. *Journal of the American Medical Association* 271 (18): 1445–1447.

Simpson, C. 2004. 'When hope makes us vulnerable: A discussion of patient healthcare provider interactions in the context of hope'. *Bioethics* 18 (5): 428–447.

Steer, B. 2007. 'Paramedics, consent and refusal – are we competent?' *Journal of Emergency Primary Health Care* 5 (1): 1–10.

United States Government Printing Office. 2000. *Code of Federal Regulations, Title 21; Food and Drugs; Part 50 – Protection of Human Subjects*. Washington: United States Government Printing Office.

Welie, S. 2001. 'Criteria for patient decision making (in)competence: A review of and commentary on some empirical approaches'. *Medicine, Health Care and Philosophy* 4 (2): 139–151.

Cite this article as: Morgans, Amee. 2010. 'Waiver of informed consent in prehospital emergency health research in Australia'. Monash Bioethics Review 29 (1): pp. 7.1 to 7.16. DOI: 10.2104/mber1007.