보호 크림 효능 평가 방법의 개발과 적용

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= Abstract =

Development and Application of Efficacy Evaluation Techniques for Barrier Creams

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Background: Barrier creams are essential for the protection against irritant material which may be in contact with skin. The evaluation techniques for barrier creams are not fully established, so many methods have been used. We applied efficacy evaluation methods to barrier creams for the first time in Korea.

Method: In the first experiment, four kinds of irritants were applied and occluded by large Finn chamber in 20 volunteers after the application of barrier creams or moisturizer. Assessment of irritation was carried out every day, after which barrier creams and moisturizer were applied again. Experiments were performed from Monday to next Friday with a break in Sunday. Irritation was assessed by visual scoring, laser Doppler flowmetry (LDF), transepidermal water loss (TEWL), and erythema index (EI). On the control sites only irritants were applied for the same periods. In the second experiment, only irritants were applied in the first 3 days, and thereafter barrier creams and moisturizers (without irritants) were applied every day to know whether the effects of them were due to the protection from irritants or to the promotion of wound healing.

Results: In the first experiment, all 3 creams were effective against NaOH. Good effects were shown also in case of SLS. But they were not successful in the protection from lactic acid or toluene. Among non-invasive measurements, the order of sensitivity was TEWL, LDF and EI. No wound healing effect of three creams was demonstrated in the second experiment.

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서론

산업장에서 접촉성 피부염을 예방하는 것은 무엇보다 먼저 자극물질과의 접촉을 피하는 것이다. 만일 자극물질에 노출을 피할 수 없는 경우 이를 위해서 보호구나 보호외의 적용이 가장 좋다고 할 수 있으나 이것조차 사용될 수 없는 상황에서는 보호크림(barrier cream)을 바르는 것이 차선책이다. 보호크림은 도포시에 피부에 얇은 막을 형성하여 자극인자와의 직접 작용과 독성물질의 경피흡수를 막는데 목적이 있다.

외국의 경우 여러종류의 다양한 보호크림이 적합한 임상실험에 거쳐 판매되고 있는데 반해, 우리나라에서는 보호크림에 대한 연구가 미미한 실정으로 아직까지 보호크림의 평가방법에 대해 구체적으로 연구되지 않았다. 이에 저자들은 향후 보호크림 개발시 평가방법으로서 유용한 모델을 확립하고자 본 연구를 시행하였다. 자원을 대상으로 한 본 연구에서 첫번째 실험에서는 여러 자극물질 도포시에 수증도의 보호크림의 효과를 알아보았으며(제1실험) 두번째 실험에서는 이러한 보호크림의 효과가 자극의 방지에 의한 것인지, 아니면 창상 치유능력에 기인한 것인지를 알아보고자 하였다(제2실험).

연구 대상 및 방법

1. 연구 대상

40명의 자원자를 대상으로 연구를 시행하였다. 이들은 18세에서 25세 사이의 건강한 성인 남자로 실험에 본 실험과 이에 수반될 수 있는 부작용에 대해 충분히 설명을 듣고 동의서에 의하여 생명을 잃을 위험을 대상으로 하였다. 피부 혹은 전신 알레르기 병력이 없는 자만을 대상으로 하였고, 그의 시험에 영향을 줄 피부 질환이 있는 자는 대상에서 제외하였다. 제1실험에 20명, 제2실험에 20명을 배정하였다.

2. 자극물질

NaOH(Sigma사, 미국), sodium lauryl sulfate (Sigma사, 미국, 이하 SLS라 약함), lactic acid (Junsei chemical사, 일본), toluene(Showa chemical사, 일본)의 4가지를 이용하였다. NaOH, SLS, lactic acid는 친수성 물질로 3차 인용수에 녹여서 사용하였다. SLS는 피부장벽 파괴 효과가 큰 대표적 계면 활성제이고, lactic acid는 적절한 농도에서는 피부자극 및 박탈(exfoliation) 효과를 가질 수 없으나 두 פרי와 같은 세포간의 결합력(cohesion)을 떨어뜨리는 다른 피부 박탈 물질과 다른 점이 알려져 있다. Toluene는 유기성 용매로 올리브 오일에 녹여 사용하였다. 이들 4가지 물질의 적절 자극농도는 각자 자극을 대한 수차례의 예비 실험을 통해서 정하였는데 1-2일간에 바로 강한 자극이 나타나지 않고 수일간에 관통이 지속적으로 도포할 경우 자극을 주는 적절 농도로 하였다. NaOH의 경우 1.25%(w/v), SLS는 0.75%(w/v), lactic acid는 7.5%(w/v), toluene는 40%(v/v)로 정하였다.

3. 보호크림의 선정

우리나라에서 현재 사용되고 있는 보호크림의 수는 매우 적다. 본 실험에서는 2가지의 보호크림과 1가지의 보습제를 이용하였다. A크림은 W사에 생산되는 보호크림의 일종으로 glycerin이 주요분이었으며 oil

4. 연구 방법

1) 제1실험
대상자의 등에 지름 15mm의 원을 일렬로 4개씩 4 줄, 총 16개를 그린 후에 보호크림을 바르기 전 각 부위에 대해 육안적 평가와 비침습적 기구를 가지고 기분값을 측정하였다. 그후에 보호크림 3종을 각 줄에 도포하고 나머지 4개의 원은 대조군으로 나머져 놓았다. 보호크림은 50μℓ를 각각의 원안에 수술흥 정관을 금 손가락으로 문질러 바르도록 하였다. 보호크림의 정량은 Microman® pipette(Gilson medical electronics, 프랑스)를 이용하였다. 자극물질은 filter paper가 포함된 large Finn chamber (지름 12mm, Epitest Oy, 핀란드)내에 50μℓ를 넣어뜨린 다음 Scanpor tape로 chamber를 고정하였다. 대조군 부위에는 보호크림을 바르지 않은채 자극물질만을 도포하였다. 첫날 부작용 후 다음날 피해자가 방문할 때까지 붓어 놓았고, 피해자가 오면 chamber를 제거하고 30분 이상 경과한 뒤 자극평균을 평가하였다. 자극 평가가 끝나면 첫날과 같이 보호크림을 바른 채 자극을 도포하여 붓어 놓았다. 이러한 과정을 매일 반복하였는데 첫주는 월병일에 시작해서 월병일까지 계속하였으며 토요일에는 chamber를 떼고 자극평균을 평가한 뒤 토요일과 일요일에는 보호크림과 자극물질 모두 바르지 않았다. 둘째 주 월요일부터 독감을 치는 첫번째 주와 독감은 과정을 반복하였으며 월요일에는 chamber를 떼고 자극평균을 측정하는 것으로 실험을 마무리하였다.

2) 제2실험
첫 주 3일간은 보호크림을 바르지 않고, 자극물질만을 large Finn chamber를 통해 도포하였으며, 이 후에는 자극물질 도포는 중단하고 매일 보호크림만 바른 것을 둘째주 목요일까지 계속하였다. 자극평균의 평가도 제1실험에서는 같은 방법으로 시행하였다. 대조군은 3일간 자극후에 아무것도 바르지 않는 것으로 하였다.

5. 자극 정도의 평가

육안적 관찰과 3가지의 비침습적 측정기구를 이용하였다.

1) 육안적 관찰

다음과 같이 5단계로 등급을 정하였다.
0: 육안적으로 보아 아주 반응이 없는 경우
1: 피부가 반짝이나거나 겉이 인지될만한 홍반이 있는 경우
2: 경미한 홍반
3: 중등도의 홍반, 부분은 경계부위에서 겉이 인지될 수는 있다. 구진도 나타날 수 있다.
4: 심한 홍반과 함께 전체적으로 부족이 동반된 경우
5: 심한 홍반과 심한 부족이 동반된 경우, 수포가 동반될 수도 있다.

2) 피부 혈류 측정(Laser Doppler Flowometry, 이하 LDF라 약함)

Laser Doppler flowmeter PF2(Perimed사, 스페인)을 이용하였다. 이것은 진피 유두하 모세혈관 (dermal subpapillary capillary)의 혈류량을 알아낸다.
3) 경피적 수분손실(transepidermal water loss, 이하 TEWL이라고 약함)
Evaporimeter EP1(Servomed사, 스웨덴)을 이용하여 피부 각질층의 장벽기능 정도를 알아보았다. 주위 온도에 민감하게 작동하므로 실내온도는 23℃±2℃를 유지하였다. 습도는 35±2%를 유지하였다.

4) 홍반 지수(erythema index, 이하 EI라고 약함)
dermatospectrophotometer(Cortex technology 사, 랑마크)를 이용하여 피부에 나타나는 홍반 정도를 객관적으로 평가하였다.

6. 자극의 중단

육안적 관찰 소견으로 grade 4에 이르게 되거나 피험자가 심한 불편을 호소하는 경우 자극물질과 보호 크림을 더 이상 바르는 것을 중지하였다.

7. 통계적 분석

Repeated measure ANOVA를 이용하여 대조군 부위와 각 자극물질 및 크림 도포군 부위간의 측정치의 차이를 분석하였다. P value가 0.05 미만이면 통계적으로 유의한 것으로 간주하였다.

결 과

1. 제1실험

1) NaOH로 자극한 경우
Table 1에 나타낸바와 같이 3가지 크림 모두 대조군에 비해 육안적 소견 및 TEWL, LDF 측정시에 유의한 효과가 있는 것으로 나타났다 (P<0.001). 대조군의 경우에는 피험자 개인에 따른 정도의 차이는 있었으나 대개 자극물질 도포 5~8일이면 육안적 관찰에서 grade 4에 달했기 때문에 그 이후는 더 이상 자극물질을 도포하지 않았다. EI 측정시에서는 대조군과 3가지 크림을 바른 부위 사이에 통계적으로 유의한 차이가 없었다. TEWL 측정에서 C크림은 B 크림이나 A크림에 비해 유의한 효과가 있었으며 (P<0.05, Fig. 1), 이것은 육안적 소견에서도 마찬가지였다. A크림과 B크림을 비교했을 때 TEWL에서는 B크림이 유의하게 효과적인 것으로 나타났으나 (P<0.05) 육안적 소견이나 LDF에서는 차이를 볼 수 없었다.

Table 1. The differences of severity of irritation between controls and treated groups

<table>
<thead>
<tr>
<th>irritants</th>
<th>Visual score</th>
<th>TEWL</th>
<th>LDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>NaOH</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>SLS</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>lactic acid</td>
<td>(−)</td>
<td>(−)</td>
<td>(+)</td>
</tr>
<tr>
<td>toluene</td>
<td>(−)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

(+): There are statistically significant differences between treated groups and controls. (p<0.05)

(−): There are no significant differences between treated groups and controls. (p≥0.05)
2) SLS로 자극한 경우
대조군에는 자극물질을 바른 후 평균 7일이 경과하면 육안적 소견상 grade 4에 도달하여 자극물질 도포를 중단하였으므로 대조군과 3가지 크림을 바른 부위사이에 통계적 비교는 7일까지만 가능하였다. TEWL 측정과 육안적 소견 관찰결과(Fig. 2)는 3가지 크림 모두 효과가 있는 것으로 나타났으나(P<0.001), LDF 측정에서는 A크림의 효능이 없는 것으로 나타났다(Table 1). A, B, C 크림 사이에 TEWL, LDF, 육안적 소견에서 유의한 차이의 차이가 없었다. EI 측정에서는 각 부위사이에 통계적인 차이가 없었다.

3) Lactic acid로 자극한 경우
TEWL 측정(Fig. 3)과 육안적 관찰에서 대조군과 C크림사이에는 유의한 차이가 있었으나(P<0.01),
Fig. 3. The results of TEWL measurement in barrier cream-treated groups compared with control group in case of irritation by lactic acid

Fig. 4. The results of LDF measurement in barrier cream-treated groups compared with control group in case of irritation by toluene

다른 크림들은 대조군에 비해 유의한 효과를 보여주지 못했다(Table 1). LDF와 EI 측정에서는 대조군과 각 크림을 바른 부위사이에 유의한 차이가 없는 것으로 나타났다. A, B, C 각 크림은 서로간에 4가지 측정 방법 모두에서 차이를 볼 수 없었다.

4) Toluene으로 자극한 경우
유안적 관찰에서는 대조군과 3가지 크림을 도포한 부위사이에 유의한 차이가 있었으나(P < 0.01), LDF (Fig. 4), TEWL, EI 등의 비침습적 측정방법으로는 통계적으로 유의한 차이를 볼 수 없었다(Table 1). A,
B, C 각 크림을 바른 부위사이에는 4가지 측정방법 모두에서 유의한 차이가 없었다.

2. 제2실험

4가지 자극물질 모두에서 대조군과 A, B, C 크림을 바른 부위간의 통계적으로 유의한 차이가 없었다.

고찰

각종 피부 도포 약제와 마찬가지로 보호크림도 그 효과 평가 방법이 통일되어 있는 것은 아니다. Mahmoud 등은 일제기 평가방법으로 보호크림 및 자극물질 도포 후 조직검사를 시행하는 방법을 제시한 바 있으나 이는 guinea pig를 대상으로 한 것이었고 첨부법의 원칙으로 민감도는 관계없이 인체에서도 적용가능한 것은 아니다. Marks 등은 1986년에 피부 표면 생검(skin surface biopsy)과 laser Doppler를 이용한 피부 혈류량 측정 등 2가지를 제시한 바 있으며 최근에도 이 방법은 종종 쓰이고 있는 경우가 있다. 그 후 Frosch는 수년간의 체계적인 연구로 반복 자극 시험(repetitive irritation test)을 이용한 보호크림의 효과 평가에 우월하다는 것을 명백히 보였다. 먼저 guinea pig을 대상으로 방법을 확립하고 가능성을 보인 다음, 인간에서도 이 방법을 이용하여 자극을 적게 주면서도 보호크림의 효과를 평가할 수 있었다고 주장하였다. 이 연구들은 동물 large Finn chamber를 이용한 자극물질을 매일 30분 동안 12일간 도포하여 자극을 일으키면서 보호크림의 효과를 평가하는 방법을 사용하였다. 이 방법은 정상적인 접촉에 의한 자극을 일으킬만한 적은 농도로 시간만 자극하여 보호크림의 예방효과를 보는 것이었다.

대부분의 방법들이 하루 혹은 2주내에 결과를 알아 본 것인데 반해 수개월간 계속 보호크림을 바르게 하면서 자극물질을 도포하거나 혹은 일정 작업환경에 노출되도록 한 연구도 있었다. 이 방법은 실제 상황 속에서의 보호크림 효과를 알아보는 장점은 있으나, 시간이 너무 오래 걸리는 피험자들에 대한 잠재적인 감독이 어려운다는 단점이 있다. 이러한 표본은 적은 비용으로도 수행할 수 있는 비첨적이고, 보호크림의 안전성 만족리도 치고 있다. 또한 실제 보호크림이 사용될 자극물질에 노출, 시간이 실험에서 사용되는 방법과 부합되어야 설득력이 있다고 생각된다.

본 실험에서는 2주간 실험을 진행한 후에 측정을 하고 보호도를 측정하였다는 점에서는 최근 외국의 다른 연구에서의 동일한 기존의 반복 자극 시험에서는 30 분간 Finn chamber을 사용 후 때를 매일 반복하여 자극을 유발한 반면, 저자는 자극물질을 large Finn chamber에 담은 체로 거의 하루종일 붙여 놓는다는 점이 달랐다. 이 방법은 환자에게 다소 불편하기는 하나 실제 작업장에서 보호크림을 도포하고 자극물질에 착용할 때 연속적으로 자극물질과 피부가 접촉될 수 있다는 점에서 좀 더 실제 상황에 가깝다고 사료된다.

본 실험에서 자극물질은 α-hydroxy acid, 알칼리, 계면활성제, 유키용제 등을 대표하는 것으로 이는 다른 연구에서 사용된 바 있으나 이번 실험에서는 자극 시간이 길기 때문에 적당한 농도로 구하기 위하여 자극물질은 수회의 예비실험을 실시하였다. 그 결과 각각의 자극물질에 대해 적정농도를 구하였는데, 외국의 연구에서 보호 시의 30분간 자극시에 적당한 농도는 많은 차이를 보여주었다. 적정 농도는 자극 부위, 자극 시간, 자극물질 도포방법 등에 의해 영향을 받으며 피부형(skin type), 모발이나 눈의 색깔 등에는 무관한 것으로 알려져 있다. 보호크림을 바르지 않은 대조군의 경우 연구가 끝나기 전까지 모든 피험자에서 육안 등급이 4 이상으로 되어 중등도 자극을 중단하였다. 일부 대상자에서는 피부색소침착, 반혼 등의 흰종증도 관찰되었다. 이것은 하루 30분 간 자극한 방법에서도 보고된 사실로 특히, 사람을 대상으로 한 실험적 연구에서의 문제점이 된다. 따라서, 농도 또는 자극 시간의 조절이 필요할 수 있으며, 이 실험의 결과는 향후 이 분야의 연구에 기초자료로 활용될 수 있다고 본다.

4가지 자극물질 중에 NaOH에 대해서는 보호크림
인 A, B 크림과 보습제인 C크림이 모두 우수한 보호 효과를 나타내었다. SLS 역시 A크림이 LDF로 측정했을 때의 것과 비교하여 3가지 종류의 크림이 모두 효과를 보여주었다. 그러나 lactic acid에 대한 효과는 보호크림의 A, B 크림에서는 없었는데 반해 보습제인 C크림에는 있는 것으로 나타났다. Toluene에 대해서는 모든 크림의 용해가 조건에서는 대조군보다 효과를 나타낸 것으로 보였으나, 비침습적 방법에서는 이를 실패해주지 못했다. 자극물질에 따른 보호크림의 효과는 일반적으로 친수성(hydrophilic)크림은 oil-in-water emulsion 형태로서 지료성 자극물질에 사용하며, 소수성(hydrophobic)크림은 water-in-oil emulsion 형태로서 수용성 자극물질을 취급하는 작업자에 적합한 것으로 알려져 있으나, 오히려 이와 반대되는 결과를 보인 경우도 있었다. 본 실험이나 사용한 보호크림 및 보습제도 모두 oil-in-water emulsion 형태였으나 수용성 자극물질인 NaOH에 가장 보호 효과가 큰 것으로 나타났다. 따라서 보호크림의 성장을 먼저 지금하고 실제 작업장에서 접촉하는 자극물질의 종류에 따라 보호크림을 결정해야 하며, 적합하지 못한 보호크림은 오히려 자극을 악화시킬 수 있다는 점에서 소중스러운 사항이 필요하다고 사료된다. 그리고 본 연구에서는 전반적으로 보호크림보다 보습제인 C크림의 효과가 다소 좋은 것으로 나타났다. 보습제는 그 염증성과 중 seja 보호크림과 겪치는 것으로 알려져 있으며, 각질층에 흡수되어 우수한 피부상피 보호효과를 갖는다는 것이 알려져 있다. 보습제의 종류에 따라서는 이러한 효과가 보호크림으로 시험할 때는 일부 함유도로 보수할 수도 있다고 사료되는 바, 이러한 점은 향후 보호크림 및 보습제의 종류를 다수로 실험하여 결과를 내릴 필요가 있다고 생각한다.

본 연구에서는 4가지의 자극 측정방법을 사용하였는데, E1을 측정하는 dermatospectrophotometer는 자극을 잘 반영하지 못하였다. Table 1에 나타낸 바와 같이 용해성 관화 소견이 자극을 가장 반영하였다고 할 수 있고, TEWL, LDF는 이와 같은 결과의 대체적으로 다른 연구들21,22와 일치하였는데 비침습적 측정 방법의 장점은 간편적인 정량이 가능하고, 정밀한 자극장에도 그 정도를 잘 반영한다는 점이다. 이 기구들은 상호 보완적이며 모든 자극물질에 같은 반응을 나타내어지는 않는다. 또한 기계를 조작하는 연구자 및 기계자체에 따라 차이가 있을 수 있다는 점을 항상 고려해야 한다23.

요 약

연구배경:
보호크림의 사용은 직접적으로 자극물질에 노출되는 경우에 필수적인 것으로 인식되고 있다. 그러나 보호크림의 헹양 평가방법은 연구가 아니라 다른 국내에서는 아직 그 평가방법 및 효능에 대해 알아 본 바가 없기에 저자들은 이에 대해 연구를 시행하였다.

방 법:
제1자원에서는 2가지 보호크림 및 1가지 보습제를 비교하였는데, 이들을 도포하고 나서 30분 경과 후 4가지 자극물질을 large Finn chamber로 밀폐하였으나, 실험 자극성을 관찰하고 다시 보호크림, 보습제 및 자극물질을 도포하는 것을 반복하였다. 첫 번째 실험은 급성에들게 하지 않는 실험을 위해 실험용이들로 실험한 것으로 하였다. 자극물질은 용해성 화학, 피부 혈류 측정(LDF), 경피적 수분 손실(TEWL), 혈관 지수(EI)의 4가지로 이용하였다. 대조군은 아무것도 도포하지 않고 자극물질만 도포하는 것으로 하였다. 제2실험에서는 처음 3일간은 보호크림 및 보습제를 도포하지 않고 자극물질만 도포했으며 이후에는 보호크림 혹은 보습제만을 발라서 보호크림이나 보습제의 효과가 자극의 반응에 미치는 것임을 청상 차유능력에 기인한 것이지 않아 보고가 하였다.

결 과:
제1실험에서는 NaOH로 자극한 경우에 3가지 크림 모두에서 효과가 있는 것으로 나타났으며, 이러한 효과는 SLS에 대해서도 비슷하였다. lactic acid나 toluene에 대해서는 뚜렷한 효과를 보여주지 못하였.
다. 비침습적 측정방법에서는 TEWL, LDF, EI 순으로 민감한 것으로 나타났다. 제2 실험에서는 3가지 크림이 항상최효과가 없는 것으로 나타나서 제1 실험의 결과가 자극의 방지에 의한 것임을 보여 주었다.

결론:

이상의 결과로 볼때 상기 방법은 보호크림의 평가에 유용하게 이용될 수 있으리라 생각되며 자극물질에 따라 보호크림의 효능이 달라질음을 알 수 있었다.

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ii. INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.
1. GLOSSARY

1.1 Adverse Drug Reaction (ADR)
In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established; all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Amendment (to the protocol)
See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)
Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 Approval (in relation to Institutional Review Boards)
The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 Audit
A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit Certificate
A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit Report
A written evaluation by the sponsor's auditor of the results of the audit.
1.9 Audit Trial
Documentation that allows reconstruction of the course of events.

1.10 Blinding/Masking
A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 Case Report Form (CRF)
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12 Clinical Trial/Study
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 Clinical Trial/Study Report
A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14 Comparator(Product)
An investigational or marketed product (ie, active control), or placebo, used as a reference in a clinical trial.

1.15 Compliance (in relation to trials)
Adherence to all the trial—related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality
Prevention of disclosure, to other than authorized individuals, of a sponsor’s proprietary information or of a subject’s identity.

1.17 Contract
A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 Coordinating Committee
A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.
1.19 Coordinating Investigator
An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20 Contract Research Organization (CRO)
A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 Direct Access
Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 Documentation
All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 Essential Documents
Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see the ICH Guideline for Guideline on Essential Documents for the Conduct of a Clinical Trial).

1.24 Good Clinical Practice (GCP)
A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)
An independent data—monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 Impartial Witness
A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent from and any other written information supplied to the subject.

1.27 Independent Ethics Committee (IEC)
An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility
it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28 Informed Consent
A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29 Inspection
The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or contract research organization’s (CRO’s) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical)
Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional Review Board (IRB)
An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 Interim Clinical Trial/Study Report
A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational Product
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 Investigator
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.
1.35 Investigator/Institution
An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36 Investigator’s Brochure
A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

1.37 Legally Acceptable Representative
An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject’s participation in the clinical trial.

1.38 Monitoring
The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39 Monitoring Report
A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor’s SOPs.

1.40 Multicentre Trial
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41 Nonclinical Study
Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)
The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record
See Source Documents.

1.44 Protocol
A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment
A written description of a change(s) to or formal clarification of a protocol.

1.46 Quality Assurance (QA)
All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice
(GCP) and the applicable regulatory requirement(s).

1.47 Quality Control (QC)
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 Randomization
The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 Regulatory Authorities
Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 Serious Adverse Event(SAE) or Serious Adverse Drug Reaction(Serious ADR)
Any untoward medical occurrence that at any dose:
- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect
  (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51 Source Data
All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents
Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53 Sponsor
An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 Sponsor-Investigator
An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an
agency). The obligations of a sponsor—investigator include both those of a sponsor and those of an investigator.

1.55 Standard Operating Procedures (SOPs)
Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 Subinvestigator
Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 Subject/Trial Subject
An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 Subject Identification Code
A unique identifier assigned by the investigator to each trial subject to protect the subject’s identity and used in lieu of the subject’s name when the investigator reports adverse events and/or other trial related data.

1.59 Trial Site
The location(s) where trial—related activities are actually conducted.

1.60 Unexpected Adverse Drug Reaction
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator’s Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61 Vulnerable Subjects
Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects)
The physical and mental integrity of the subjects participating in a clinical trial.
2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities
3.1.1
An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2
The IRB/IEC should obtain the following documents:
Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator’s Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator’s current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may require to fulfill its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:
- Approval/favorable opinion;
- Modifications required prior to its approval/favorable opinion;
- Disapproval/negative opinion; and
- Termination/suspension of any prior approval/favorable opinion.

3.1.3
The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4
The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5
The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects.

3.1.6
When a non-therapeutic trial is to be carried out with the consent of the subject’s legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7
Where the protocol indicates that prior consent of the trial subject or the subject’s legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).
3.1.8
The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9
The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 Composition, Functions, and Operations

3.2.1
The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.
(b) At least one member whose primary area of interest is in a nonscientific area.
(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial—related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2
The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3
An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4
Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5
The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6
An IRB/IEC may invite nonmembers with expertise in special areas for assistance.
3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1
Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2
Scheduling, notifying its members of, and conducting its meetings.

3.3.3
Conducting initial and continuing review of trials.

3.3.4
Determining the frequency of continuing review, as appropriate.

3.3.5
Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

3.3.6
Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.

3.3.7
Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8
Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).

(c) All adverse drug reactions (ADR’s) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9
Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.
(c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors, or regulatory authorities to provide copies of its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1
The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2
The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

4.1.3
The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4
The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5
The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
4.2 Adequate Resources

4.2.1
The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2
The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3
The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4
The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial—related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1
A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial—related medical (or dental) decisions.

4.3.2
During and following a subject’s participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3
It is recommended that the investigator inform the subject’s primary physician about the subject’s participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4
Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject’s rights.

4.4 Communication with IRB/IEC

4.4.1
Before initiating a trial, the investigator/institution should have written and dated approval/favorable
opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2
As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3
During the trial the investigator/institution should provide to the IRB/IEC all documents subject to its review.

4.5 Compliance with Protocol

4.5.1
The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement.

4.5.2
The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

4.5.3
The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4
The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement; and, if required,
(c) To the regulatory authority(ies).
4.6 Investigational Product(s)

4.6.1
Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2
Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3
The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4
The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5
The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6
The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).
4.8 Informed Consent of Trial Subjects

4.8.1
In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2
The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form, and written information should receive the IRB/IEC’s approval/favorable opinion in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3
Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4
None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject’s legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5
The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject’s legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

4.8.6
The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the subject or the subject’s legally acceptable representative and the impartial witness, where applicable.

4.8.7
Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject’s legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject’s legally acceptable representative.
4.8.8
Prior to a subject’s participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9
If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject’s legally acceptable representative, and after the subject or the subject’s legally acceptable representative has orally consented to the subject’s participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject’s legally acceptable representative, and that informed consent was freely given by the subject or the subject’s legally acceptable representative.

4.8.10
Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.
(b) The purpose of the trial.
(c) The trial treatment(s) and the probability for random assignment to each treatment.
(d) The trial procedures to be followed, including all invasive procedures.
(e) The subject’s responsibilities.
(f) Those aspects of the trial that are experimental.
(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
(j) The compensation and/or treatment available to the subject in the event of trial—related injury.
(k) The anticipated prorated payment, if any, to the subject for participating in the trial.
(l) The anticipated expenses, if any, to the subject for participating in the trial.
(m) That the subject’s participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject’s original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent
form, the subject or the subject’s legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject’s identity will remain confidential.

(p) That the subject or the subject’s legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject’s willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial—related injury.

(r) The foreseeable circumstances and/or reasons under which the subject’s participation in the trial may be terminated.

(s) The expected duration of the subject’s participation in the trial.

(t) The approximate number of subjects involved in the trial.

4.8.11
Prior to participation in the trial, the subject or the subject’s legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject’s participation in the trial, the subject or the subject’s legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12
When a clinical trial (therapeutic or nontherapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject’s legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject’s understanding and, if capable, the subject should assent, sign and personally date the written informed consent.

4.8.13
Except as described in 4.8.14, a nontherapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14
Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.

(b) The foreseeable risks to the subjects are low.

(c) The negative impact on the subject’s well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.
Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15
In emergency situations, when prior consent of the subject is not possible, the consent of the subject’s legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject’s legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject’s legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

4.9.1
The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRF’s and in all required reports.

4.9.2
Data reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3
Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators’ designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRF's made by sponsor’s designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4
The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5
Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the
investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6
The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7
Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1
Where required by the applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2
The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8), and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 Safety Reporting

4.11.1
All serious adverse events (SAE's) should be reported immediately to the sponsor except for those SAE's that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2
Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3
For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional re-
quested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1

If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2

If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3

If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator/Institution

Upon completion of the trial, the investigator should, where required by the applicable regulatory requirements, inform the institution, and the investigator/institution should provide the sponsor with all required reports, the IRB/IEC with a summary of the trial’s outcome, and the regulatory authority(ies) with any report(s) they require of the investigator/institution.

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOP’s to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
5.1.2
The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3
Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4
Agreements, made by the sponsor with the investigator/institution and/or with any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1
A sponsor may transfer any or all of the sponsor’s trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2
Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3
Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4
All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial-related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1
The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRF’s
and planning the analyses to analyzing and preparing interim and final clinical trial/study reports.

5.4.2
For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol, and conduct.

5.5 Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee

5.5.1
The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2
The sponsor may consider establishing an independent data monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3
When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor’s established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

(b) Maintain SOP’s for using these systems.

(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

5.5.4
If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5
The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.
5.5.6
The sponsor, or other owners of the data, should retain all of the sponsor—specific essential documents pertaining to the trial. (See 8. “Essential Documents for the Conduct of a Clinical Trial.”)

5.5.7
The sponsor should retain all sponsor—specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8
If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor—specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9
If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the appropriate regulatory authorities.

5.5.10
Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11
The sponsor—specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12
The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed (see 4.9.5).

5.6 Investigator Selection

5.6.1
The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If a coordinating committee and/or coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor’s responsibility.
5.6.2
Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3
The sponsor should obtain the investigator's/institution's agreement:

(a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC;

(b) To comply with procedures for data recording/reporting and

(c) To permit monitoring, auditing, and inspection (see 4.1.3, 4.1.4 and 4.5.1).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Duties and Functions

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 Compensation to Subjects and Investigators

5.8.1
If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2
The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3
When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
5.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)), should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1
The sponsor should obtain from the investigator/institution:
   (a) The name and address of the investigator’s/institution’s IRB/IEC.
   (b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.
   (c) Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2
If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.

5.11.3
The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/reevaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

5.12 Information on Investigational Product(s)

5.12.1
When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2
The sponsor should update the Investigator’s Brochure as significant new information becomes available. (See 7: “Investigator’s Brochure.”)
5.13 Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)

5.13.1
The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

5.13.2
The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3
The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4
In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5
If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1
The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2
The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3
The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation
thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4
The sponsor should:

(a) Ensure timely delivery of investigational product(s) to the investigator(s).
(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s). (See 8. “Essential Documents for the Conduct of a Clinical Trial.”)
(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).
(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5
The sponsor should:

(a) Take steps to ensure that the investigational product(s) are stable over the period of use.
(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1
The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2
The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 Safety Information

5.16.1
The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2
The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial,
or alter the IRB/IEC’s approval/favorable opinion to continue the trial.

5.17 Adverse Drug Reaction Reporting

5.17.1
The sponsor should expedite the reporting to all concerned investigator(s)/institution(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADR's) that are both serious and unexpected.

5.17.2
Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3
The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 Monitoring

5.18.1 Purpose
The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors.

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor’s SOP’s, GCP, and the applicable regulatory requirement(s).

5.18.3 Extent and Nature of Monitoring.
The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators’ training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.
5.18.4 Monitor's Responsibilities.

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.
(b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and these remain adequate throughout the trial period, and that the staff and facilities, including laboratories and equipment, are adequate to safely and properly conduct the trial and these remain adequate throughout the trial period.
(c) Verifying, for the investigational product(s):
   (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
   (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
   (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
   (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
   (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor's authorized procedures.
(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
(e) Verifying that written informed consent was obtained before each subject's participation in the trial.
(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
(i) Verifying that the investigator is enrolling only eligible subjects.
(j) Reporting the subject recruitment rate.
(k) Verifying that source data/documents and other trial records are accurate, complete, kept up-to-date, and maintained.
(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
(m) Checking the accuracy and completeness of the CRF entries, source data/documents, and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRF's and are consistent with the source data/documents.

(ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(iii) Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRF’s.

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRF’s.

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRF’s.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator’s trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AE’s) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, the applicable regulatory requirement(s), and indicated in the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

(p) Determining whether the investigator is maintaining the essential documents. (See 8. “Essential Documents for the Conduct of a Clinical Trial.”)

(q) Communicating deviations from the protocol, SOP’s, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 Monitoring Procedures.
The monitor(s) should follow the sponsor’s established written SOP’s as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 Monitoring Report.

(a) The monitor should submit a written report to the sponsor after each trial—site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor’s statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report by the sponsor should be documented by the sponsor’s designated representative.
5.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose.
The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOP's, GCP, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors.
(a) The sponsor should appoint individuals, who are independent of the clinical trial/data collection system(s), to conduct audits.
(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 Auditing Procedures.
(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.
(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).
(c) The observations and findings of the auditor(s) should be documented.
(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case-by-case basis, when evidence of serious GCP noncompliance exists, or in the course of legal proceedings or investigations.
(e) Where required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 Noncompliance

5.20.1
Noncompliance with the protocol, SOP's, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2
If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).
5.21 Premature Termination or Suspension of a Trial

If a trial is terminated prematurely or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial/study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial/study reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 Multicenter Trials

For multicenter trials, the sponsor should ensure that:

5.23.1
All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favorable opinion by the IRB/IEC.

5.23.2
The CRF’s are designed to capture the required data at all multicenter trial sites. For those investigators who are collecting additional data, supplemental CRF’s should also be provided that are designed to capture the additional data.

5.23.3
The responsibilities of the coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4
All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRF’s.

5.23.5
Communication between investigators is facilitated.
6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 General Information

6.1.1
Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2
Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3
Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4
Name, title, address, and telephone number(s) of the sponsor’s medical expert (or dentist when appropriate) for the trial.

6.1.5
Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6
Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable) who is responsible for all trial—site related medical (or dental) decisions (if other than investigator).

6.1.7
Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1
Name and description of the investigational product(s).

6.2.2
A summary of findings from nondclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
6.2.3
Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4
Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5
A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

6.2.6
Description of the population to be studied.

6.2.7
References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose
A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design
The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

6.4.1
A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2
A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.

6.4.3
A description of the measures taken to minimize/avoid bias, including (for example):
   (a) Randomization.
   (b) Blinding.

6.4.4
A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).

6.4.5
The expected duration of subject participation, and a description of the sequence and duration of all trial
periods, including follow-up, if any.

6.4.6
A description of the “stopping rules” or “discontinuation criteria” for individual subjects, parts of trial, and entire trial.

6.4.7
Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8
Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9
The identification of any data to be recorded directly on the CRF’s (i.e., no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1
Subject inclusion criteria.

6.5.2
Subject exclusion criteria.

6.5.3
Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/investigational product treatment.
(b) The type and timing of the data to be collected for withdrawn subjects.
(c) Whether and how subjects are to be replaced.
(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1
The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2
Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
6.6.3
Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1
Specification of the efficacy parameters.

6.7.2
Methods and timing for assessing, recording, and analyzing efficacy parameters.

6.8 Assessment of Safety

6.8.1
Specification of safety parameters.

6.8.2
The methods and timing for assessing, recording, and analyzing safety parameters.

6.8.3
Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4
The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1
A description of the statistical methods to be employed, including timing of any planned interim analysis (ses).

6.9.2
The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3
The level of significance to be used.

6.9.4
Criteria for the termination of the trial.

6.9.5
Procedure for accounting for missing, unused, and spurious data.
6.9.6
Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).

6.9.7
The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents
The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics
Description of ethical considerations relating to the trial.

6.13 Data Handling and Recordkeeping

6.14 Financing and Insurance
Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy
Publication policy, if not addressed in a separate agreement.

6.16 Supplements

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. INVESTIGATOR'S BROCHURE

7.1 Introduction
The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures. The IB
also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and nonpromotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk—benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor’s written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with GCP, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRB’s)/Independent Ethics Committees (IEC’s) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRB’s/IEC’s. In the case of an investigator-sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor—investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor—investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 General Considerations

The IB should include:

7.2.1 Title Page

This should provide the sponsor’s name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipient to treat the IB as a confidential document for the sole information and use of the investigator’s team and the IRB/IEC.
7.3 Contents of the Investigator’s Brochure.

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 Table of Contents
An example of the Table of Contents is given in Appendix 2.

7.3.2 Summary
A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction
A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g., advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation
A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies
Introduction:
The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested;
- Number and sex of animals in each group;
- Unit dose (e.g., milligram/kilogram (mg/kg));
- Dose interval;
- Route of administration;
- Duration of dosing;
- Information on systemic distribution;
- Duration of post-exposure follow-up;
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects;
  - Severity or intensity of pharmacological or toxic effects;
  - Time to onset of effects;
  - Reversibility of effects;
  - Duration of effects;
  - Dose response.

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology
A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals
A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology
A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:
- Single dose;
- Repeated dose;
- Carcinogenicity;
- Special studies (e.g., irritancy and sensitization);
- Reproductive toxicity;
- Genotoxicity (mutagenicity).

7.3.6 Effects in Humans.
Introduction:
A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results from any use of the investigational product(s) other than in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Product Metabolism in Humans
- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
  - Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
  - Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
  - Population subgroups (e.g., gender, age, and impaired organ function).
  - Interactions (e.g., product-product interactions and effects of food).
  - Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s)).

(b) Safety and Efficacy
A summary of information should be provided about the investigational product’s/products’ (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience
The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator.
This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the
available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 Appendix 1:

TITLE PAGE OF INVESTIGATOR’S BROCHURE (Example)

Sponsor’s Name:
Product:
Research Number:
Name(s): Chemical, Generic (if approved)
   Trade Name(s) (if legally permissible and desired by the sponsor)
Edition Number:
Release Date:
Replaces Previous Edition Number:
Date:

7.5 Appendix 2:

TABLE OF CONTENTS OF INVESTIGATOR’S BROCHURE (Example)

- Confidentiality Statement (optional)
- Signature Page (optional)
1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies
5.1 Nonclinical Pharmacology
5.2 Pharmacokinetics and Product Metabolism in Animals
5.3 Toxicology
6. Effects in Humans
6.1 Pharmacokinetics and Product Metabolism in Humans
6.2 Safety and Efficacy

- 117 -
6.3 Marketing Experience

7. Summary of Data and Guidance for the Investigator

NB: References on
1. Publications
2. Reports

These references should be found at the end of each chapter

Appendices (if any)

8. Essential Documents for the Conduct of Clinical Trial

8.1 Introduction

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor, and monitor. These documents are also the ones that are usually audited by the sponsor’s independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: (1) Before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution’s site and at the sponsor’s office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.
8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8.2.1 INVESTIGATOR'S BROCHURE</strong></td>
<td>To document that relevant and current scientific information about the investigational product has been provided to the investigator</td>
<td>X</td>
</tr>
<tr>
<td><strong>8.2.2 SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)</strong></td>
<td>To document investigator and sponsor agreement to the protocol/amendment(s) and CRF</td>
<td>X</td>
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<tr>
<td><strong>8.2.3 INFORMATION GIVEN TO TRIAL SUBJECT</strong></td>
<td>To document the informed consent</td>
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<tr>
<td>- INFORMED CONSENT FORM (including all applicable translations)</td>
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</tr>
<tr>
<td>- ANY OTHER WRITTEN INFORMATION</td>
<td>To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent</td>
<td>X</td>
</tr>
<tr>
<td>- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)</td>
<td>To document that recruitment measures are appropriate and not coercive</td>
<td>X</td>
</tr>
<tr>
<td><strong>8.2.4 FINANCIAL ASPECTS OF THE TRIAL</strong></td>
<td>To document the financial agreement between the investigator/institution and the sponsor for the trial</td>
<td>X</td>
</tr>
<tr>
<td><strong>8.2.5 INSURANCE STATEMENT (where required)</strong></td>
<td>To document that compensation to subject(s) for trial-related injury will be available</td>
<td>X</td>
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<tr>
<td><strong>8.2.6 SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, eg:</strong></td>
<td>To document agreements</td>
<td>X</td>
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<td>- investigator/institution and sponsor</td>
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<td>- investigator/institution and CRO</td>
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<td>- sponsor and CRO</td>
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<td>- investigator/institution and authority(ies)</td>
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<td>(where required)</td>
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</table>
| 8.2.7 | DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB)/INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:  
- protocol and any amendments  
- CRF (if applicable)  
- informed consent form(s)  
- any other written information to be provided to the subject(s)  
- advertisement for subject recruitment (if used)  
- subject compensation (if any)  
- any other documents given approval/favourable opinion | To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s) | \( X \)  
\( X \) |
| 8.2.8 | INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION | To document that the IRB/IEC is constituted in agreement with GCP | \( X \)  
(\( X \) (where required)) |
| 8.2.9 | REGULATORY AUTHORITY(IES) AUTHORIZATION / APPROVAL / NOTIFICATION OF PROTOCOL (where required) | To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s) | \( X \)  
(\( X \) (where required)) |
| 8.2.10 | CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S) | To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects | \( X \)  
\( X \) |
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<th>Title of Document</th>
<th>Purpose</th>
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<tr>
<td>8.2.11 NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/LABORATORY/TECHNICAL PROCEDURE(S) PROTOCOL</td>
<td>To document normal values and/or ranges of the tests</td>
<td>X X</td>
</tr>
<tr>
<td>8.2.12 MEDICAL/LABORATORY/TECHNICAL PROCEDURES/TESTS</td>
<td>To document competence of facility to perform required test(s), and support reliability of results</td>
<td>X X (where required)</td>
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<td>— certification or</td>
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<td>— accreditation or</td>
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<td>— established quality control and/or external quality assessment or</td>
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<td>— other validation (where required)</td>
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<tr>
<td>8.2.13 SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)</td>
<td>To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects</td>
<td>X X</td>
</tr>
<tr>
<td>8.2.14 INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)</td>
<td>To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials</td>
<td>X X</td>
</tr>
<tr>
<td>8.2.15 SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</td>
<td>To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability</td>
<td>X X</td>
</tr>
<tr>
<td>8.2.16 CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED</td>
<td>To document identity, purity, and strength of investigational product(s) to be used in the trial</td>
<td>X</td>
</tr>
<tr>
<td>Title of Document</td>
<td>Purpose</td>
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<tr>
<td>8.2.17 DECODING PROCEDURES FOR BLINDED TRIALS</td>
<td>To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment</td>
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<td>(third party if applicable)</td>
</tr>
<tr>
<td>8.2.18 MASTER RANDOMISATION LIST</td>
<td>To document method for randomisation of trial population</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(third party if applicable)</td>
</tr>
<tr>
<td>8.2.19 PRE-TRIAL MONITORING REPORT</td>
<td>To document that the site is suitable for the trial (may be combined with 8.2.20)</td>
<td>X</td>
</tr>
<tr>
<td>8.2.20 TRIAL INITIATION MONITORING REPORT</td>
<td>To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)</td>
<td>X       X</td>
</tr>
</tbody>
</table>
8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Investigator/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Institution Sponsor</td>
</tr>
<tr>
<td>8.3.1 INVESTIGATOR’S BROCHURE UPDATES</td>
<td>To document that investigator is informed in a timely manner of relevant information as it becomes available</td>
<td>X</td>
</tr>
<tr>
<td>8.3.2 ANY REVISION TO:</td>
<td>To document revisions of these trial related documents that take effect during trial</td>
<td>X</td>
</tr>
<tr>
<td>- protocol/amendment(s) and CRF</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- informed consent form</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- any other written information provided to subjects</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- advertisement for subject recruitment (if used)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>8.3.3 DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</td>
<td>To document that the amendment(s) and/or revision (s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).</td>
<td>X</td>
</tr>
<tr>
<td>- protocol amendment(s)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- revision(s) of:</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- informed consent form</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- any other written information to be provided to the subject</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- advertisement for subject recruitment (if used)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- any other documents given approval/favourable opinion</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>- continuing review of trial (where required)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Title of Document</td>
<td>Purpose</td>
<td>Located in Files of Investigator/ Institution Sponsor</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>8.3.4 REGULATORY AUTHORITY(IES) AUTHORIZATIONS/APPROVALS/ NOTIFICATIONS WHERE REQUIRED FOR: protocol amendment(s) and other documents</td>
<td>To document compliance with applicable regulatory requirements</td>
<td>X X (where required)</td>
</tr>
<tr>
<td>8.3.5 CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB- INVESTIGATOR(S)</td>
<td>(see 8.2.10)</td>
<td>X X</td>
</tr>
<tr>
<td>8.3.6 UPDATES TO NORMAL VALUE(S)/RANGE (S) FOR MEDICAL/LABORATORY/TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL</td>
<td>To document normal values and ranges that are revised during the trial (see 8.2.11)</td>
<td>X X</td>
</tr>
<tr>
<td>8.3.7 UPDATES OF MEDICAL/LABORATORY/TECHNICAL PROCEDURES/TESTS</td>
<td>To document that tests remain adequate throughout the trial period (see 8.2.12)</td>
<td>X X (where required)</td>
</tr>
<tr>
<td>- certification or</td>
<td></td>
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<tr>
<td>- accreditation or</td>
<td></td>
<td></td>
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<tr>
<td>- established quality control and/or external quality assessment or</td>
<td></td>
<td></td>
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<tr>
<td>- other validation (where required)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.3.8 DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL—RELATED MATERIALS SHIPMENT</td>
<td>(see 8.2.15)</td>
<td>X X</td>
</tr>
<tr>
<td>8.3.9 CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS</td>
<td>(see 8.2.16)</td>
<td>X</td>
</tr>
<tr>
<td>8.3.10 MONITORING VISIT REPORTS</td>
<td>To document site visits by, and findings of, the monitor</td>
<td>X</td>
</tr>
<tr>
<td>8.3.11</td>
<td>RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To document agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- letters</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- meeting notes</td>
<td></td>
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<td></td>
<td>- notes of telephone calls</td>
<td></td>
</tr>
<tr>
<td>8.3.12</td>
<td>SIGNED INFORMED CONSENT FORMS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)</td>
<td></td>
</tr>
<tr>
<td>8.3.13</td>
<td>SOURCE DOCUMENTS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject</td>
<td></td>
</tr>
<tr>
<td>8.3.14</td>
<td>SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To document that the investigator or authorised member of the investigator's staff confirms the observations recorded</td>
<td></td>
</tr>
<tr>
<td>8.3.15</td>
<td>DOCUMENTATION OF CRF CORRECTIONS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>To document all changes/additions or corrections made to CRF after initial data were recorded</td>
<td></td>
</tr>
<tr>
<td>8.3.16</td>
<td>NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11</td>
<td></td>
</tr>
</tbody>
</table>

Locate in Files of
Investigator/
Institution Sponsor

|        | X | X |
|        | X |    |
|        | X |    | (copy) | (original) |
|        | X | X |
|        | X | X |

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<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.3.17 NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY (IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION</td>
<td>Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2</td>
<td>X X (where required)</td>
</tr>
<tr>
<td>8.3.18 NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION</td>
<td>Notification by sponsor to investigators of safety information in accordance with 5.16.2</td>
<td>X X</td>
</tr>
<tr>
<td>8.3.19 INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY (IES)</td>
<td>Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3</td>
<td>X X (where required)</td>
</tr>
<tr>
<td>8.3.20 SUBJECT SCREENING LOG</td>
<td>To document identification of subjects who entered pre-trial screening</td>
<td>X X (where required)</td>
</tr>
<tr>
<td>8.3.21 SUBJECT IDENTIFICATION CODE LIST</td>
<td>To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject</td>
<td>X</td>
</tr>
<tr>
<td>8.3.22 SUBJECT ENROLMENT LOG</td>
<td>To document chronological enrolment of subjects by trial number</td>
<td>X</td>
</tr>
<tr>
<td>8.3.23 INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE</td>
<td>To document that investigational product(s) have been used according to the protocol</td>
<td>X X</td>
</tr>
<tr>
<td>Title of Document</td>
<td>Purpose</td>
<td>Located in Files of</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
</tbody>
</table>
| 8.3.24  SIGNATURE SHEET               | To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs | X  
|                                                    |                                                                         | X                   |
| 8.3.25  RECORD OF RETAINED BODY       | To document location and identification of retained samples if assays need to be repeated | X  
| FLUIDS/TISSUE SAMPLES (IF ANY)         |                                                                         | X                   |
8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following:

<table>
<thead>
<tr>
<th>Title of Document</th>
<th>Purpose</th>
<th>Located in Files of</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.4.1 INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE</td>
<td>To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor</td>
<td>X   X</td>
</tr>
<tr>
<td>8.4.2 DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION</td>
<td>To document destruction of unused investigational products by sponsor or at site</td>
<td>X   X (if destroyed at site)</td>
</tr>
<tr>
<td>8.4.3 COMPLETED SUBJECT IDENTIFICATION CODE LIST</td>
<td>To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time</td>
<td>X</td>
</tr>
<tr>
<td>8.4.4 AUDIT CERTIFICATE(if available)</td>
<td>To document that audit was performed</td>
<td>X</td>
</tr>
<tr>
<td>8.4.5 FINAL TRIAL CLOSE-OUT MONITORING REPORT</td>
<td>To document that all activities required for trial close-out are completed, and copies of essential documents are help in the appropriate files</td>
<td>X</td>
</tr>
<tr>
<td>8.4.6 TREATMENT ALLOCATION AND DECODING DOCUMENTATION</td>
<td>Returned to sponsor to document any decoding that may have occurred</td>
<td>X</td>
</tr>
<tr>
<td>8.4.7 FINAL REPORT BY INVESTIGATOR TO IRB/ICE WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY (IES)</td>
<td>To document completion of the trial</td>
<td>X</td>
</tr>
<tr>
<td>8.4.8 CLINICAL STUDY REPORT</td>
<td>To document results and interpretation of trial</td>
<td>X   X (if applicable).</td>
</tr>
</tbody>
</table>